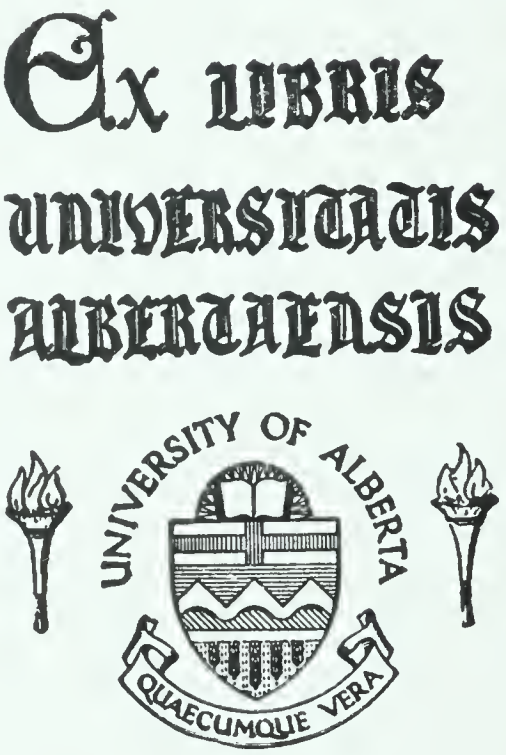

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THE UNIVERSITY OF ALBERTA

A STUDY OF THE FISCHER INDOLE SYNTHESIS

by

FRANK P. ROBINSON, JR.

A THESIS

submitted to the Faculty of Graduate Studies

in partial fulfillment of the requirements for the degree

of Doctor of Philosophy

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta

September, ~~1964~~
1964

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled

A STUDY OF THE FISCHER INDOLE SYNTHESIS

submitted by Frank P. Robinson in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

With the aim of gaining evidence in support of the proposed dienone-imine intermediate in the Fischer indole synthesis, several attempts were made to form a Diels-Alder adduct of this intermediate by the thermal cyclization of simple phenylhydrazones in the presence of the dienophiles, maleic anhydride and tetracyanoethylene. Even though cyclization of the phenylhydrazones to the corresponding indoles occurred under the conditions used, no adduct could be isolated. With maleic anhydride as the dienophile, hydrazide formation occurred instead.

Attempts to form such an adduct by cyclizing the diacetyl derivative of methyl ethyl ketone phenylhydrazone in the presence of maleic anhydride were also unsuccessful.

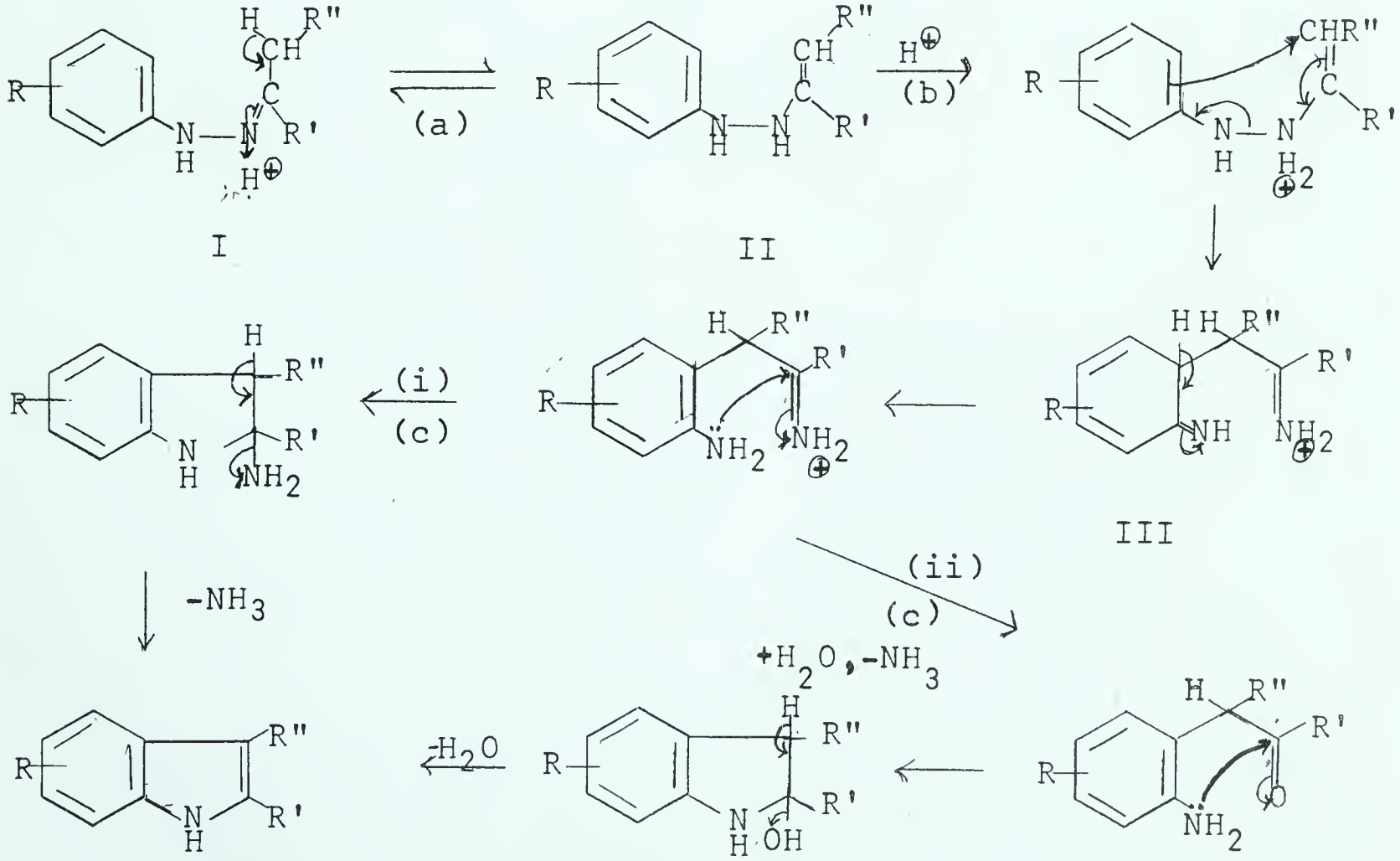
The attempted preparation of the diacetyl derivatives of 2,6-dimethylphenylhydrazones led to mono- and di-acylated 2,6-dimethylphenylhydrazines instead. An improved technique for the identification of these latter compounds was devised. This method consists of hydrogenolysis of the N—N bond of the acylated hydrazines with Raney nickel and hydrazine, followed by isolation and identification of the resulting fragments.

Finally, when N'-methyl-2,6-dicholorophenylhydrazine was prepared and condensed with cyclohexanone under mild room temperature conditions, two indoles were isolated and their structures proven by unambiguous syntheses. The formation of these products is explained in terms of the proposed dienone-imine intermediate. This also represents the first known case of such a facile non-catalytic Fischer indole synthesis.

I. Introduction

The Problem

Despite several early mechanism proposals, the presently accepted mechanism for the Fischer indole synthesis is that proposed originally by G. M. and R. Robinson. The original Robinson proposal has been modified by Allen and Wilson and more recently by Carlin and his co-workers. This mechanism, with the modifications mentioned, may be represented by the following three steps: (a) tautomerization (I⇌II); (b) rearrangement of the enehydrazine tautomer (II→III); (c) ammonia elimination [by either routes (i) or (ii)]*.



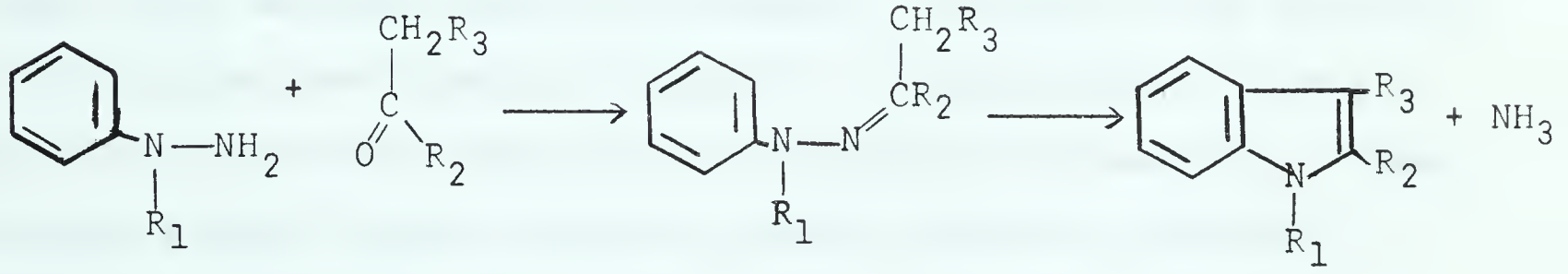
* These structures are those used by B. Robinson in Chem. Rev., 63, 373, (1963) to represent the modified mechanism.

The present problem is concerned with an attempt to gather evidence in support of the dienone-imine intermediate (III) as part of the pathway for the Fischer indole synthesis.

Literature Survey

A. General Methods of Synthesis

The Fischer indole synthesis involves the formation of an indole compound with liberation of ammonia from an appropriately substituted arylhydrazone. Generally the reaction is carried out under the influence of an acid type catalyst, but metals, anhydrous salts, and even thermal conditions have been used successfully. The reaction may be simply illustrated as follows:



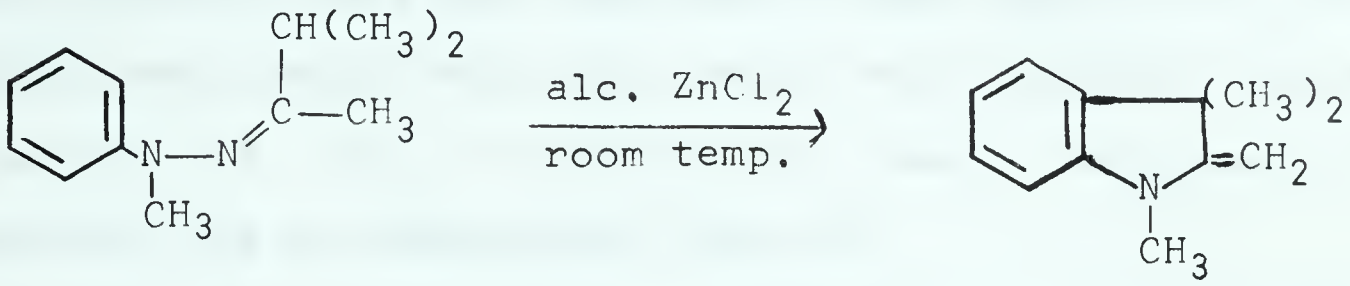
The reaction was discovered by Fischer and Jourdan (1) in 1883 when they isolated a small yield of a compound, $C_{10}H_9NO_2$, from the reaction mixture obtained by treatment of pyruvic acid 1-methylphenylhydrazone with alcoholic hydrogen chloride. This compound was later shown to be 1-methylindole-2-carboxylic acid (2). Fischer found, in further studies of the reaction, that zinc chloride was a more effective catalyst than hydrogen chloride (3). For example, Fischer found that 2-methylindole (R_1 = R_3 = H;

$R_2 = CH_3$) and skatole ($R_1 = R_2 = H$; $R_3 = CH_3$) could be prepared in good yield by the zinc chloride catalyzed ring closure of acetone phenylhydrazone and propionaldehyde phenylhydrazone, respectively.

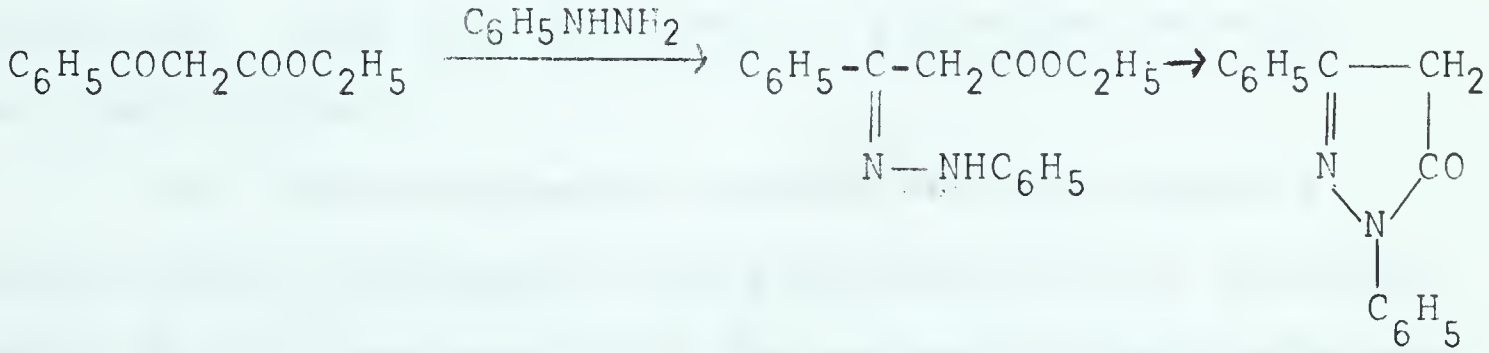
Since the initial work of Fischer, the reaction has been studied extensively and is perhaps the most versatile method of preparing indoles. These subsequent studies resulted in improved procedures and yields. For example, good yields of indoles have been obtained by heating phenylhydrazones in inert solvents such as methylnaphthalene (4). Arbuzov and Tikhvinskii (5, 6) showed that the reaction took place in the presence of only 1% of zinc chloride, and thus the large quantities of zinc chloride used by Fischer and other early workers were not necessary. Alcoholic zinc chloride (10) has also been used as catalyst. A large number of metals and metal salts have been found to catalyze the reaction. These include nickel, cobalt, copper, cuprous halides, platinum chloride, and cobalt chloride (11, 12). Concentrated sulfuric acid (7, 8), as well as alcoholic sulfuric acid (9) have proven effective as catalysts. Grammaticakis (13) showed that the reaction occurs in the presence of a variety of Grignard reagents. Witkop and his co-workers (14, 15) have demonstrated the effectiveness of the Lewis acid, boron trifluoride, as well as polyphosphoric acid as catalysts for the reaction.

There has been little correlation between phenylhydrazone structure and ease of indole formation. An unusually facile reaction occurs in some instances. For example, tetrahydrocarbazole is obtained when cyclohexanone phenylhydrazone

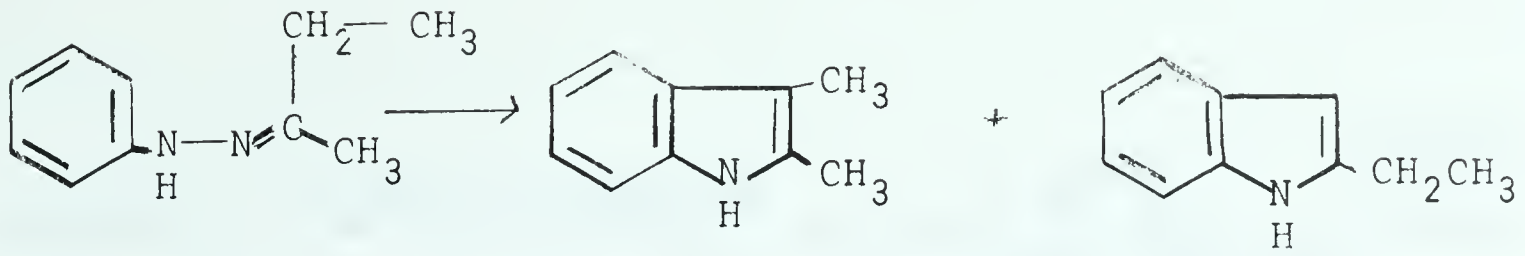
is warmed gently with aqueous hydrochloric acid. The cyclization of the methylphenylhydrazone of isopropyl methyl ketone in the presence of alcoholic zinc chloride occurs even at room temperature (16).



The Fischer synthesis has proven the most versatile and widely applicable method of preparing indoles. Despite this, however, certain exceptions and limitations have been noted. The conversion of acetaldehyde phenylhydrazone to indole, for example, has not been achieved (14). Instead of yielding indoles, the phenylhydrazones of β-keto esters are more prone to form pyrazolones.

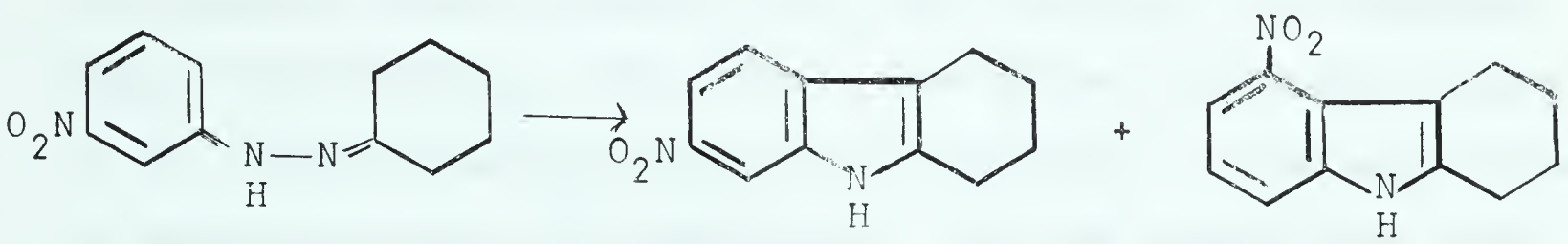


With the arylhydrazones of unsymmetrical ketones, two modes of cyclization are possible and one would expect a mixture of two products.



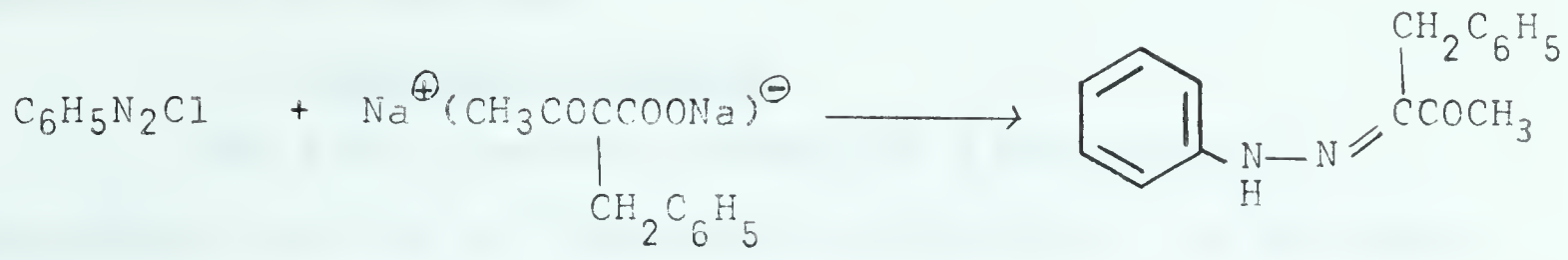
Both products have been isolated in some cases (25), but instances in which only one product was identified are more numerous (18 - 22). In still other cases, the course of the reaction was not determined (23, 24).

Cyclization of meta-substituted phenylhydrazones can yield both 4- and 6-substituted indoles. In some such cases, both possible products have been isolated and identified. For example, cyclohexanone m-nitrophenylhydrazone has been found to yield both 5-nitro- and 7-nitro-1,2,3,4-tetrahydrocarbazole (28 - 30).

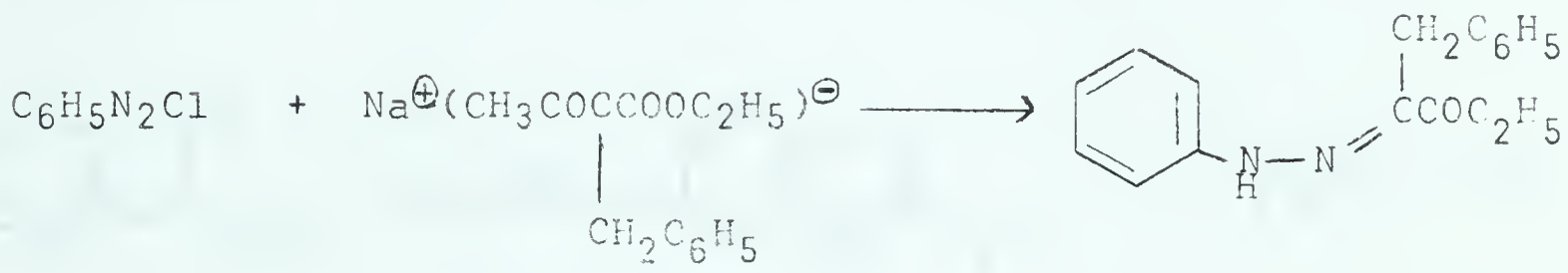


In some other cases (26, 27), product structures were not firmly established.

The Japp-Klingemann reaction (31) has proved a valuable aid to the Fischer indole synthesis for it provides a method for the preparation of the necessary phenylhydrazones from phenyldiazonium chlorides and the sodio derivatives of either β-keto acids or esters.



IV V



VI VII

In the first instance involving the salt of the carboxylic acid, (IV), the reaction proceeds with a loss of the carboxyl group to yield the hydrazone (V), whereas in the case wherein the carboxyl group is esterified (VI), the acyl is eliminated giving the hydrazone (VII) (32). Some interesting applications of the Japp-Klingemann synthesis may be found in the preparation of phenylhydrazones of α-ketoadipic acid and esters from sodio cyclopentanone-2-carboxylate (33, 34), of o-nitrophenylhydrazones of monoalkylated acetoacetic esters (35), in the synthesis of physostigmol ethyl ether (36), and in the synthesis of tryptophane (37).

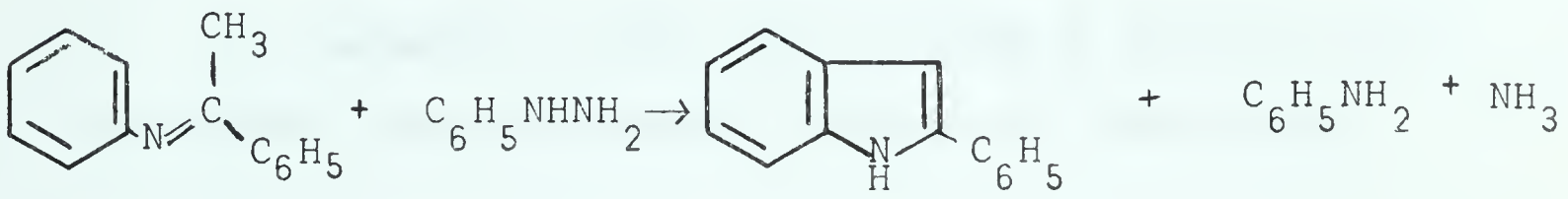
B. Mechanism Studies

During the last fifty years, the nature of the mechanism of the Fischer indole synthesis has been the subject of much research effort. Four distinct mechanisms have been

proposed for the reaction.

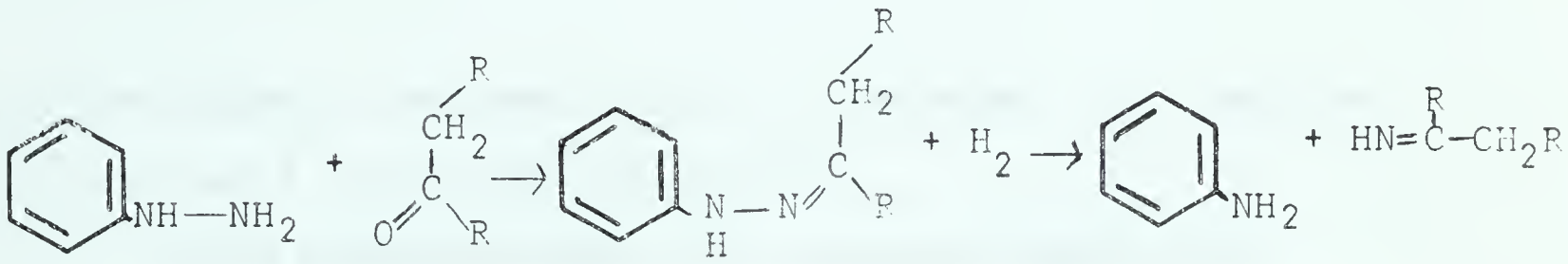
1. Reddelien Mechanism

The first reported attempt at a mechanistic explanation was that of Reddelien in 1912 (38). On the basis of his discovery of the oxidation of the anil of acetophenone by the action of phenylhydrazine to yield 2-phenylindole,

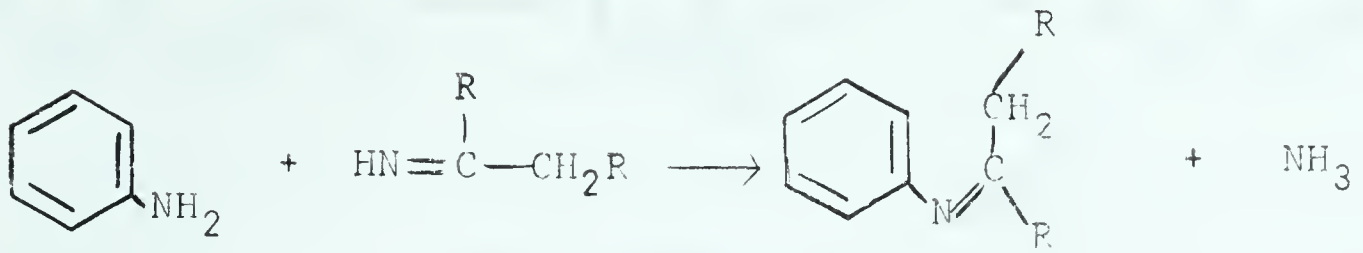


he proposed a mechanism which may be described as involving three separate stages:

a. Reduction of the phenylhydrazone with simultaneous oxidation of stage c.



b. Elimination of ammonia from the products of stage a to yield the anil.



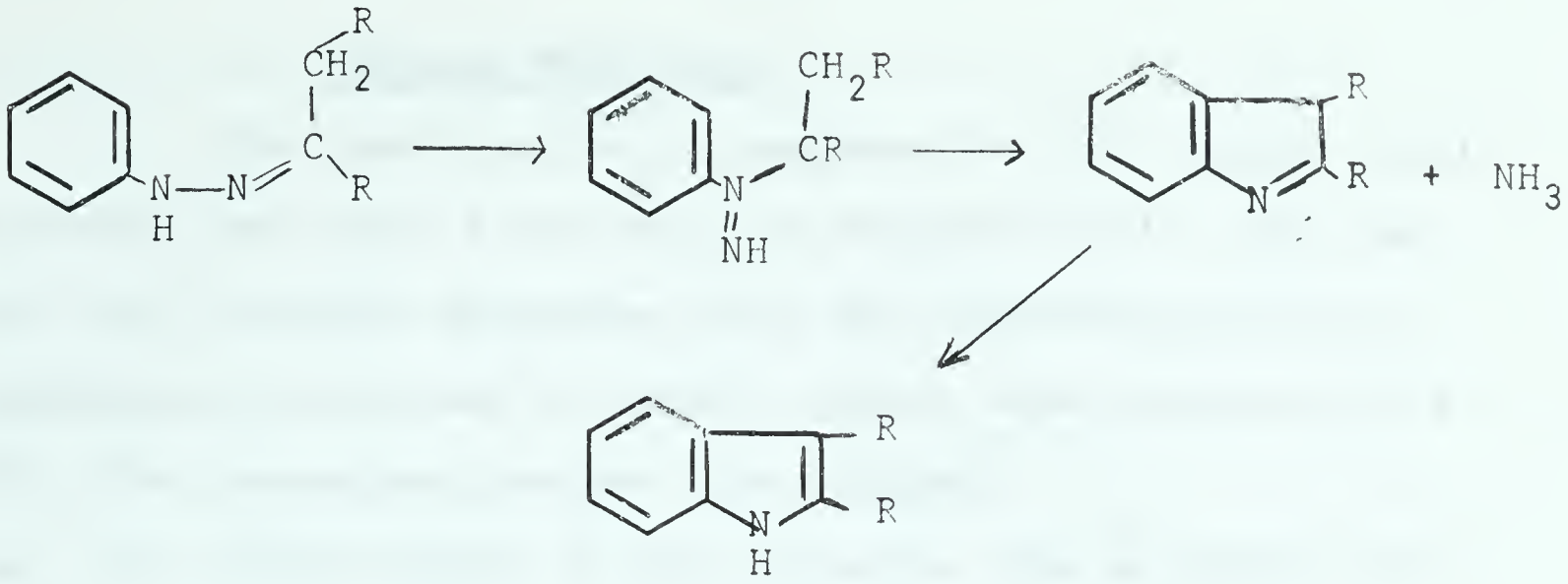
c. Oxidation of the anil of stage b by the action of the original phenylhydrazone to yield the indolenine,

which undergoes a tautomeric shift of hydrogen from position 3 to position 1, producing the indole.

This mechanism does not adequately explain the formation of 1-alkylindoles and was criticized on this basis by Robinson and Robinson (39), Bodforss (40), and Campbell and Cooper (41).

2. Bamberger-Landau Mechanism

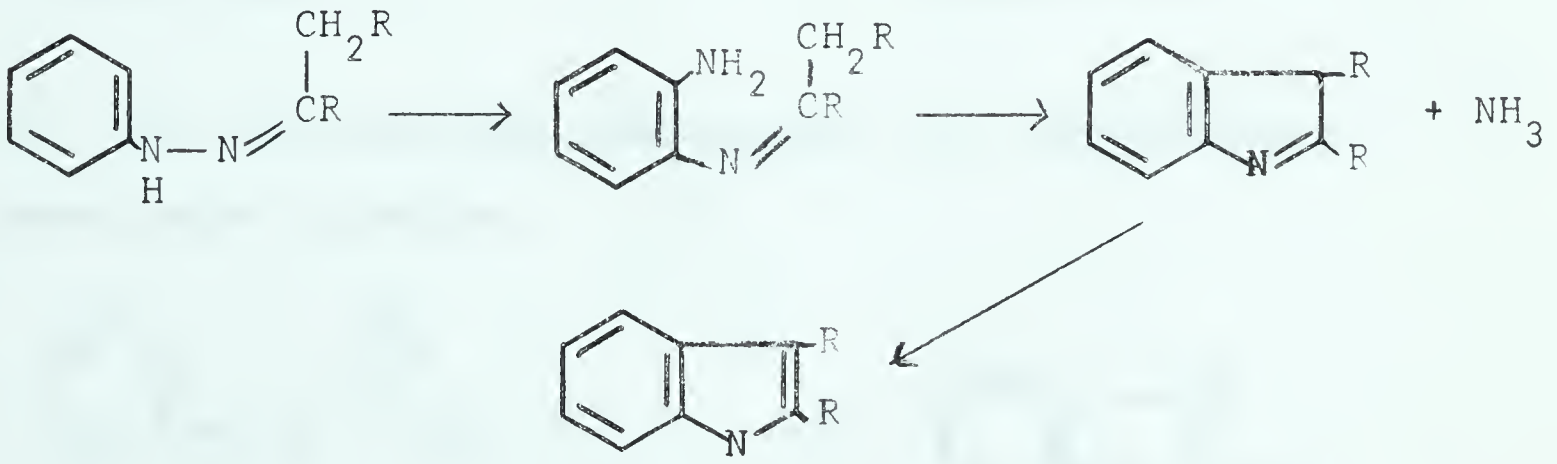
The second mechanism, proposed by Bamberger and Landau (42), involves rearrangement of the phenylhydrazone to an unlikely species containing a pentacovalent nitrogen atom.



Like the Reddelien mechanism, this mechanism also suffers from its inability to explain the formation of 1-alkyl phenylhydrazones (43).

3. Cohn Mechanism

In the third proposal, Cohn (44) suggested an ortho-semidine rearrangement of the phenylhydrazone followed by elimination of ammonia.



In addition to its failure to account for the formation of 1-alkylindoles, the Cohn mechanism predicts that p-substituted phenylhydrazones would yield 6-substituted indoles upon cyclization. In actual fact, 5-substituted indoles are obtained.

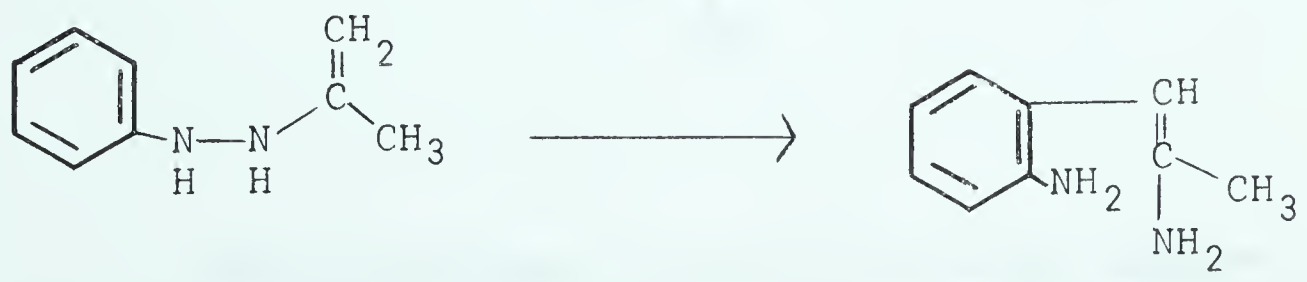
4. Robinson Mechanism

The fourth mechanism proposed for the Fischer indole synthesis was that of Robinson and Robinson (39). This was the first proposed mechanism which was consistent with all experimental facts and it rapidly gained wide acceptance (45 - 47). The mechanism involved three stages:

(a) The transformation of the hydrazone into an unsaturated hydrazine, which is the isomeric change of an enimic into an enamic modification. This is assumed to occur by the addition of the acid reagent and loss of a proton by the addition product.

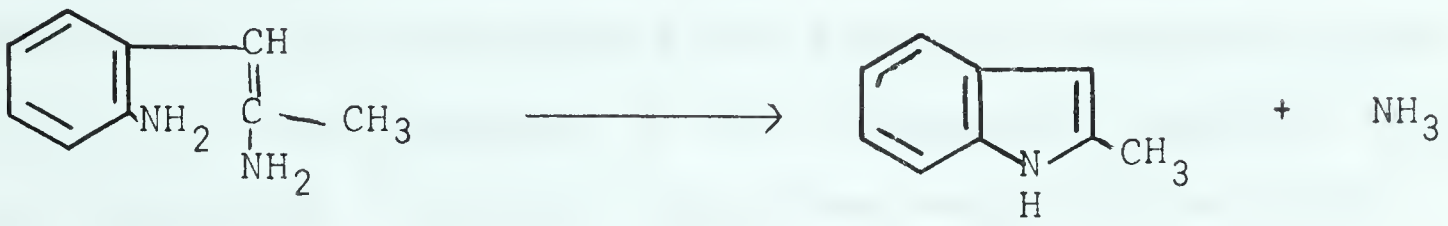
enimic form enamic form

(b) The benzidine-type rearrangement of the resulting unsaturated hydrazine.

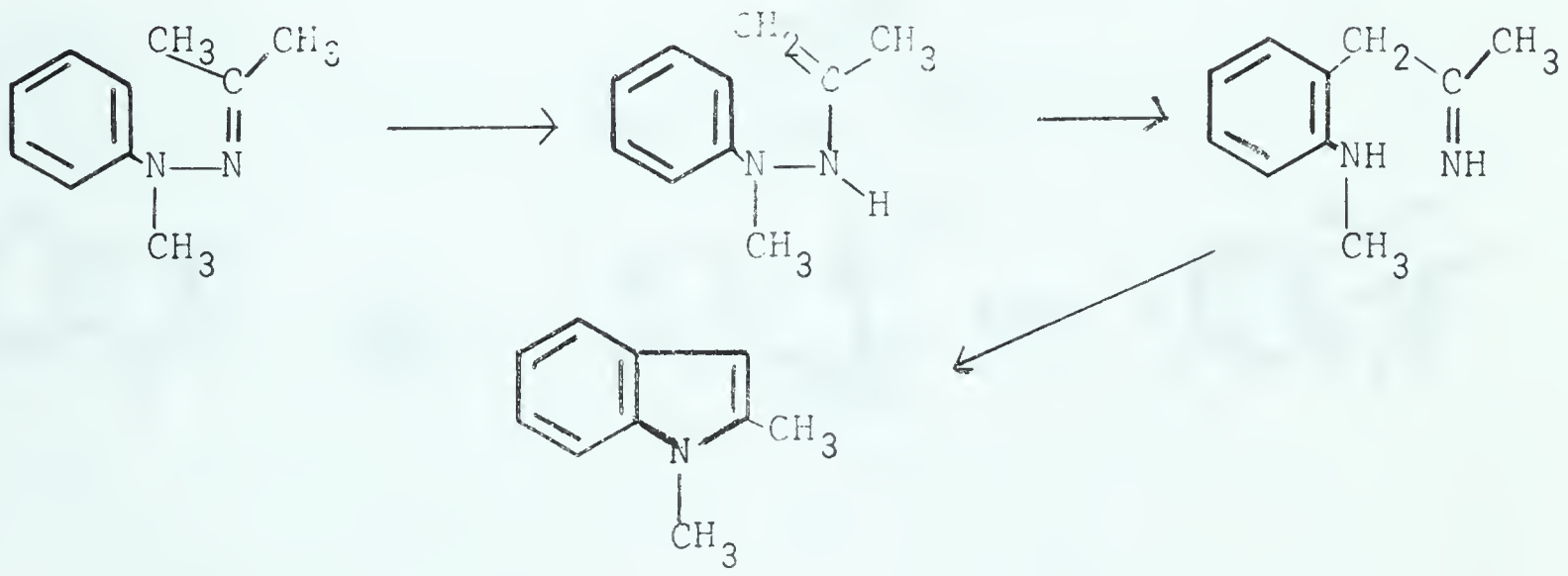


(c) Ring-formation by elimination of ammonia from the product

(analogous to the formation of piperidine from the hydrochloride of pentamethylene diamine).

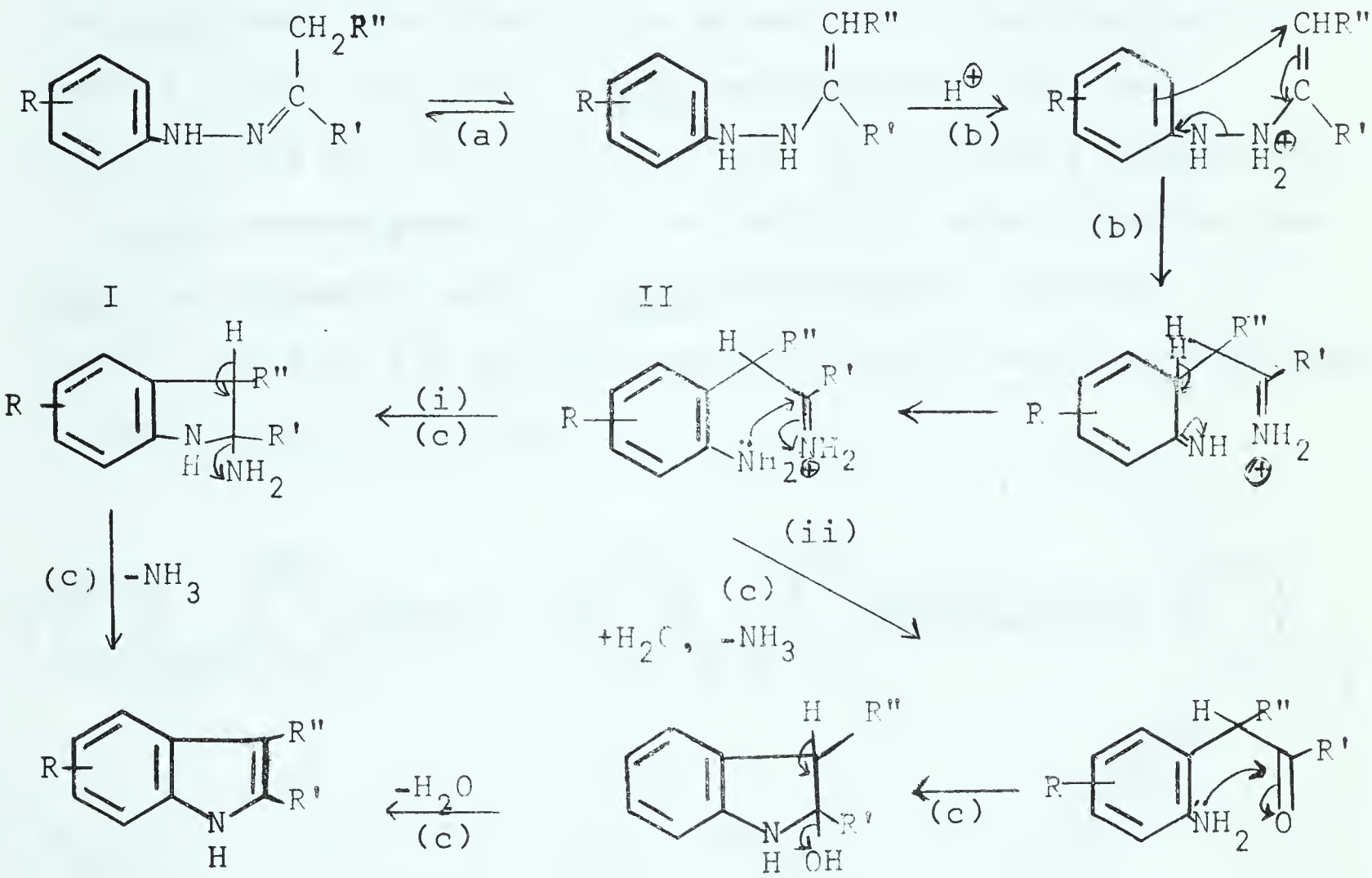


Unlike the three preceding mechanisms, the Robinson mechanism does adequately account for the formation of N-alkylindoles from secondary hydrazines.



Allen and Wilson in 1943 (49) added support to the Robinson mechanism by demonstrating that the nitrogen atom remote from the aromatic ring was indeed the one lost as ammonia in the Fischer cyclization. The first interpretation of the

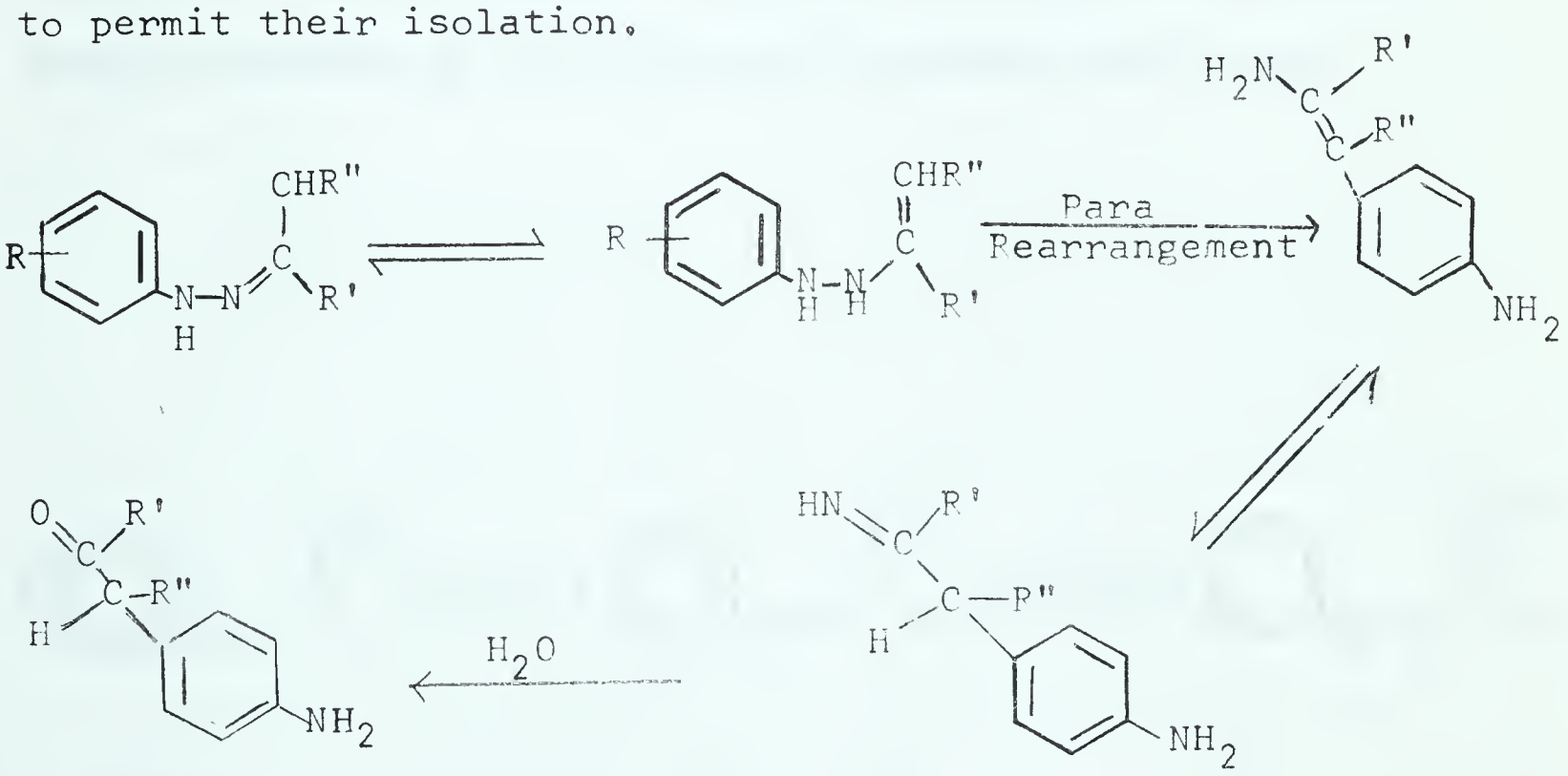
Robinson mechanism in terms of modern electronic theory was made by Carlin and Fischer in 1948 (50). These authors represented the mechanism, which encompasses the ideas of Allen and Wilson and the original Robinson proposal, as consisting of the following three steps: (a) tautomerization (I⇌II); (b) rearrangement of the enehydrazine tautomer (II→III); (c) elimination of ammonia [by either routes (i) or (ii)].



The three main stages of the foregoing mechanism are essentially the same as those suggested by Robinson and Robinson (39). Arbuzov has pointed out, however, that the idea

of an ortho-benzidine rearrangement as part of the mechanism did not originate with Robinson, but was first suggested by Brunner in 1898 (51) when he discovered that o-diaminodiphenyl could be converted into carbazole.

Although the Robinson mechanism met with general acceptance, it was not completely devoid of criticism. Hollins (53) objected to the idea of the rearrangement step being of the ortho-benzidine type on the grounds that there had been no reports of the isolation of para-rearrangement products. Robinson (39) met this criticism with the following suggestions: (1) ortho-rearrangement would be sterically more favorable than para-rearrangement, and (2) para-rearrangement products, if formed, would be too unstable under the usual reaction conditions to permit their isolation.



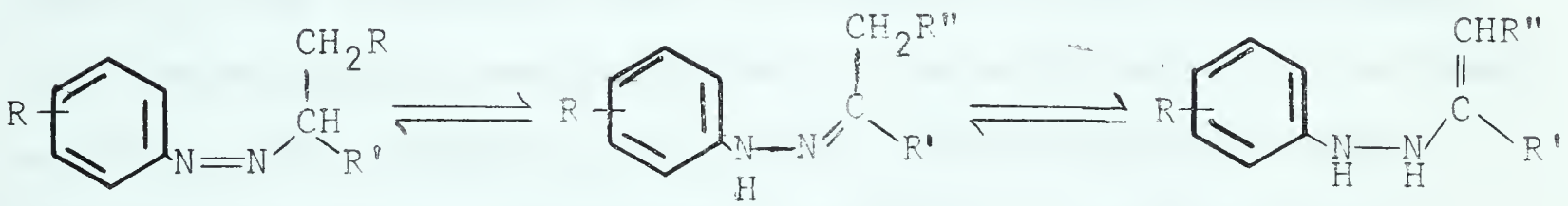
The three main stages of the Robinson mechanism have been supported by an imposing body of experimental evidence

since its intial proposal. A summary is presented in the following sections.

(a) Existing Evidence for the Various Steps Suggested in the Revised Robinson Mechanism.

i. Tautomerization [step (a)]

The original idea of the enehydrazine form of the phenylhydrazone as an intermediate in the Fischer synthesis came when Robinson (39) suggested that "the ease of the Fischer reaction of different phenylhydrazones might vary in the same way as does the ease or extent of enolization of the various ketones from which those phenylhydrazones were derived." Robinson found, for example, that phenylacetaldehyde phenylhydrazone reacts far better than does acetophenone phenylhydrazone. Later workers envisioned the tautomerization of phenylhydrazones as involving the following equilibria:



VIII IX X

These equilibria involve the possible isomerization of arylhydrazones among the hydrazone (IX), azo (VIII), and enehydrazine (X) tautomers. There was considerable controversy

concerning attempts to determine the structures of the various tautomers and their relative stabilities.

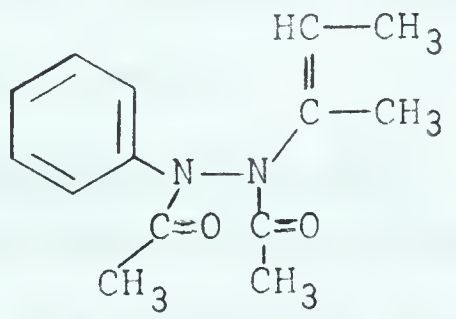
In 1947, Grammaticakis (55) suggested a serious discrepancy in all the earlier work on this problem. Prior to this, no one had studied any one tautomer which might not contain amounts of the other forms in equilibrium with each other. Consequently, Grammaticakis (55) prepared an azo compound incapable of isomerization to the other two forms and used this compound as a standard for comparison with various phenylhydrazones by means of ultraviolet and visible spectra. From these studies, he concluded that phenylhydrazones in solution exist in equilibrium with small quantities of the azo tautomer. Unfortunately, this work was later misinterpreted (56, 57) as evidence for the existence of the enehydrazine tautomers, although the work in question showed no such evidence (58).

Arbuzov and Kitaev (59) attempted to obtain further information concerning the tautomerization of phenylhydrazones from a study of polarographic data. On the basis of their results, they concluded that (a) aliphatic ketone phenylhydrazones were actually enehydrazines in the solid state or in fresh solutions; (b) aldehyde and aromatic phenylhydrazones were hydrazones; and (c) tautomorism proceeds in solutions from enehydrazine to hydrazone to azo forms.

In more recent studies, O'Connor and Rosenbrook (60, 61) questioned the validity of Arbuzov and Kitaev's conclusions. They felt that an unwise choice of reference

compounds and experimental conditions had been made and that a more careful spectral study was warranted. Using different reference compounds, they examined the ultraviolet, infrared, and nuclear magnetic resonance spectra of a number of phenylhydrazones. From their results they concluded that phenylhydrazones of aliphatic ketones and aldehydes originally exist as the hydrazone tautomer and that the conversion of the hydrazone form to the more stable azo tautomer is rapid in solution. In no instance was there any evidence found for the existence of the enehydrazine tautomer in neutral solutions of phenylhydrazones in non-polar solvents. The possibility of it existence in polar solvents or at elevated temperatures was not ruled out, however.

The most direct evidence for the existence of the enehydrazine tautomer as an intermediate in the Fischer reaction was obtained by Suvorov and co-workers (62). When those workers refluxed methyl ethyl ketone phenylhydrazone in acetic anhydride in the presence of catalytic amounts of p-toluenesulfonic acid, compound XI was obtained in good yield.



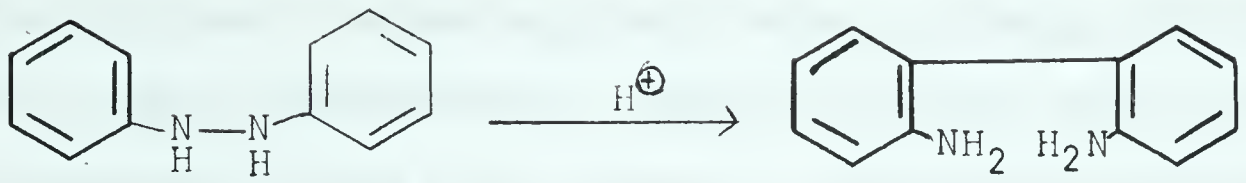
XI

Thus, they succeeded in isolating the enehydrazine tautomer

by trapping it as its diacetyl derivative. By refluxing with sulfuric acid, the acetylated enehydrazine XI could be cyclized to 2,3-dimethylindole in excellent yield. These workers then felt that the behavior of the methylphenylhydrazone of methyl ethyl ketone under analogous conditions would be of interest. When the methylphenylhydrazone of methyl ethyl ketone was acetylated, five products were isolated from the reaction mixture (63). These products were shown to be N-methylacetanilide, β-acetyl-α-methyl-α-phenylhydrazine, and 5-, 6-, and 7-acetyl-1,2,3-trimethylindole. No acetyl phenylhydrazone was isolated. Suvorov (63) explained the difference in behavior of these two hydrazones in terms of the free electron pairs on the two nitrogen atoms. In the case of the phenylhydrazone of methyl ethyl ketone, the reaction stops at the stage of the diacetyl derivative of the enhydrazine because the free electron pairs on both nitrogen atoms are fixed by acetylation. In the case of the methylphenylhydrazone, the electron pair on the nitrogen directly attached to the benzene ring remains free and thus facilitates the rearrangement to 1,2,3-trimethylindole. The three acetyl-1,2,3-trimethylindoles are said to arise by acetylation after the ring closure to 1,2,3-trimethylindole.

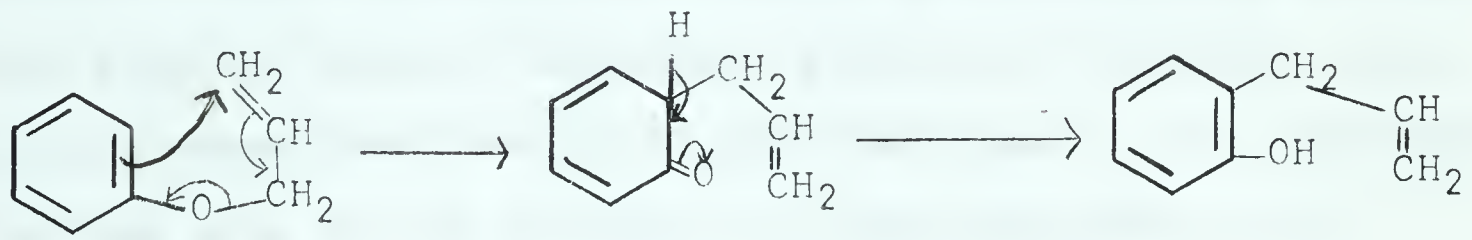
ii. Rearrangement [step (b)]

Analogies have been drawn between the rearrangement of the enehydrazine to the diamine in the Fischer indole synthesis and other molecular rearrangements. Both Brunner (66) and Robinson (39) suggested that this step in the Fischer synthesis was analogous to the ortho-benzidine rearrangement.

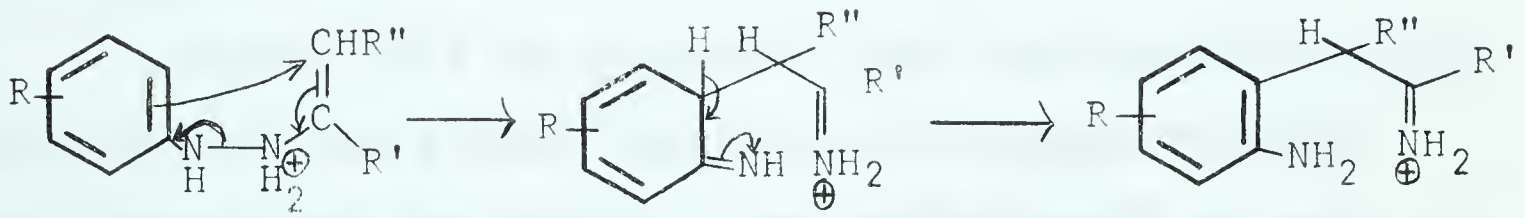


The Benzidine Rearrangement

More recently, Carlin (50) suggested that the reaction is perhaps more analogous to the ortho-Claisen rearrangement as shown below.



The ortho-Claisen Rearrangement

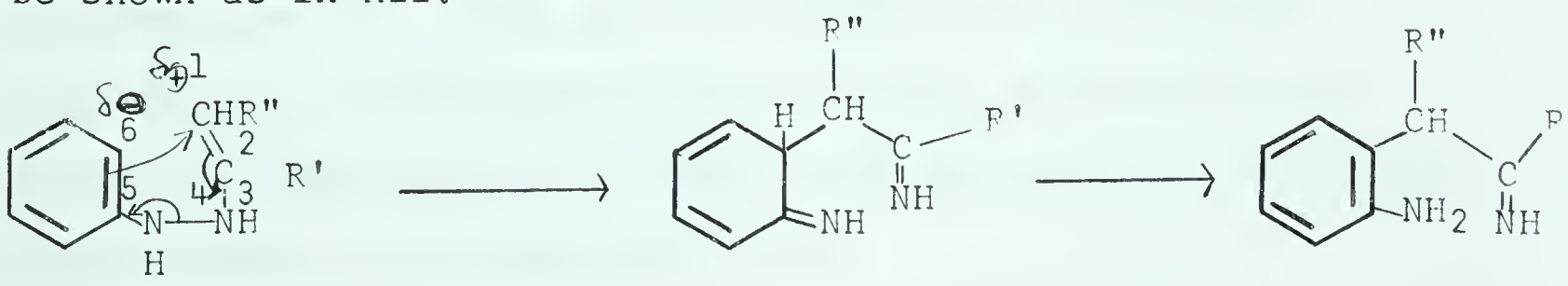


The Fischer Indole Synthesis

The benzidine rearrangement is acid catalyzed and it has been shown (67) that both nitrogen atoms are protonated

prior to rearrangement. This might well be the case in the acid-catalyzed Fischer synthesis also, although this has not been clearly demonstrated. Carlin's analogy with the Claisen rearrangement seems more general. Although the Claisen rearrangement has most often been carried out thermally (68), accumulating evidence shows that is is also subject to catalysis by acidic species (69). On the basis of Wolff's observation in 1912 (70) that distillation of acetophenone phenylhydrazone gave a low yield of 2-phenylindole, Fitzpatrick and Hiser (71) have successfully cyclized several phenylhydrazones to the corresponding indoles by refluxing in solvents such as ethylene glycol, diethylene glycol, or tetralin. Some phenylhydrazones have been thermally rearranged to the corresponding indoles even in the presence of sodium hydroxide (72). Thus it seems that both the Claisen rearrangement and the Fischer indole synthesis are facilitated by protonation or acidic catalysis, and both are possible by thermal means only, bringing the analogy between the reactions even closer.

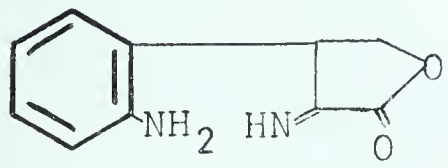
Arbuzov (59) has suggested that rearrangement of the enehydrazine in the Fischer synthesis, the ortho-benzidine rearrangement, and the ortho-Claisen rearrangement are all cases of intramolecular rearrangement in polarized 1,6-conjugated systems. This polarization in the enehydrazine tautomer may be shown as in XII.



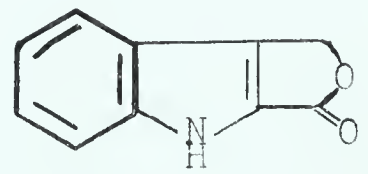
XII XIII XIV

Protonation or complex formation would enhance the polarization of XII, leading to rearrangement, with subsequent aromatization to XIV. Arbuzov refers to the polarization of XII as "'the moving force' of the conversion occurring in a Fischer reaction" (59).

Evidence in support of the intermediate imine XIV was obtained by Plieninger (73) when he attempted to effect the Fischer cyclization of α-keto- γ-butyrolactone phenylhydrazone. By passing hydrogen chloride into an alcoholic solution of the phenylhydrazone, he isolated a compound which he postulated to be the hydrochloride of XV. That XV was in fact an intermediate in the reaction was shown by heating XV to obtain the indole XVI (74).

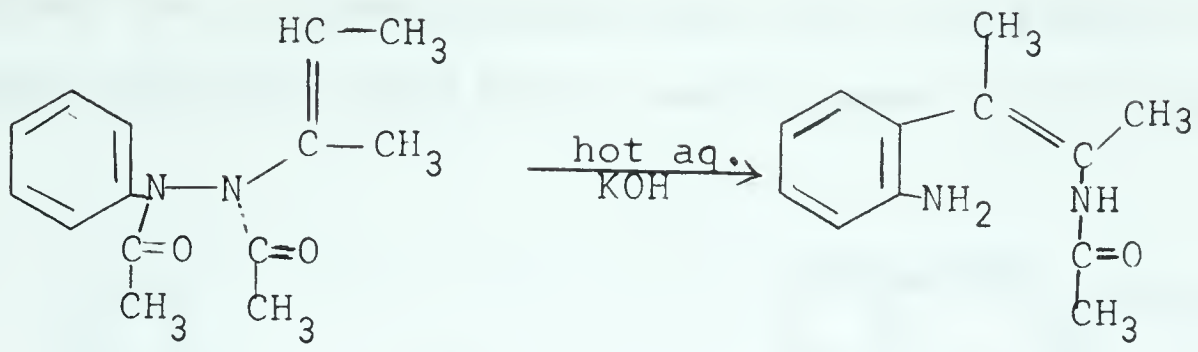


XV



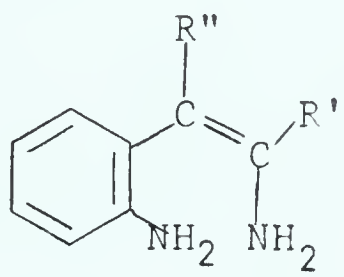
XVI

Suvorov (62) questioned the assignment of structure XV on the basis of some methods used in its verification, but succeeded himself in isolating a compound corresponding to the imine intermediate XIV. When Suvorov treated the diacetylated enehydrazine XI with potassium hydroxide, he obtained the monoacetyl derivative XVII which could be converted to 2,3-dimethylindole on treatment with acid.



XI XVII

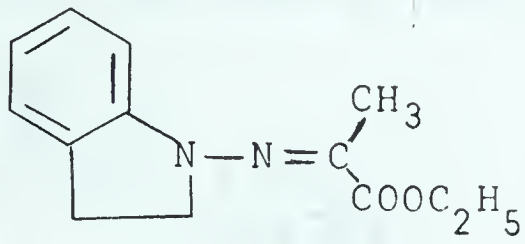
Although the stability of XVII might be due to the fact that it is acetylated, its isolation suggests that Arbuzov (59) was incorrect in his claim that postulation of the diamine XVIII was unneccessary in the Robinson mechanism.



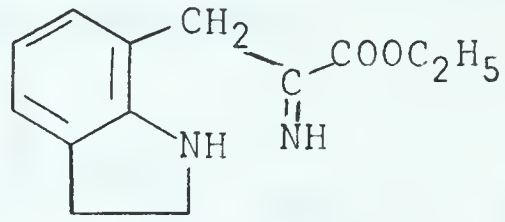
XVIII

Rapoport (75) obtained further evidence in support of the imine intermediate (XIV) by subjecting the hydrazone XIX, from 1-aminoindoline and ethyl pyruvate, to conditions of the Fischer reaction. He had postulated that as a consequence of the existence of the intermediate XX, five-membered indole formation would be difficult in this case and the presence of the carbethoxy group would cause ring closure to take an alternative course and form a six-membered ring. Indeed, he

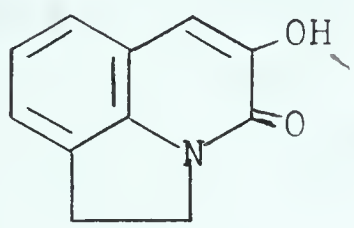
isolated the 3-hydroxy-2-quinolone XXI as the major product of this reaction along with a small amount of the indole XXII.



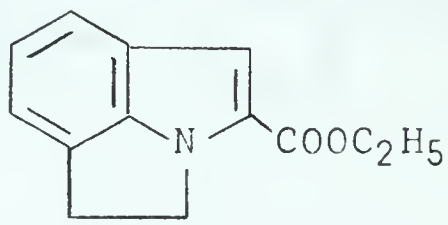
XIX



XX



XXI

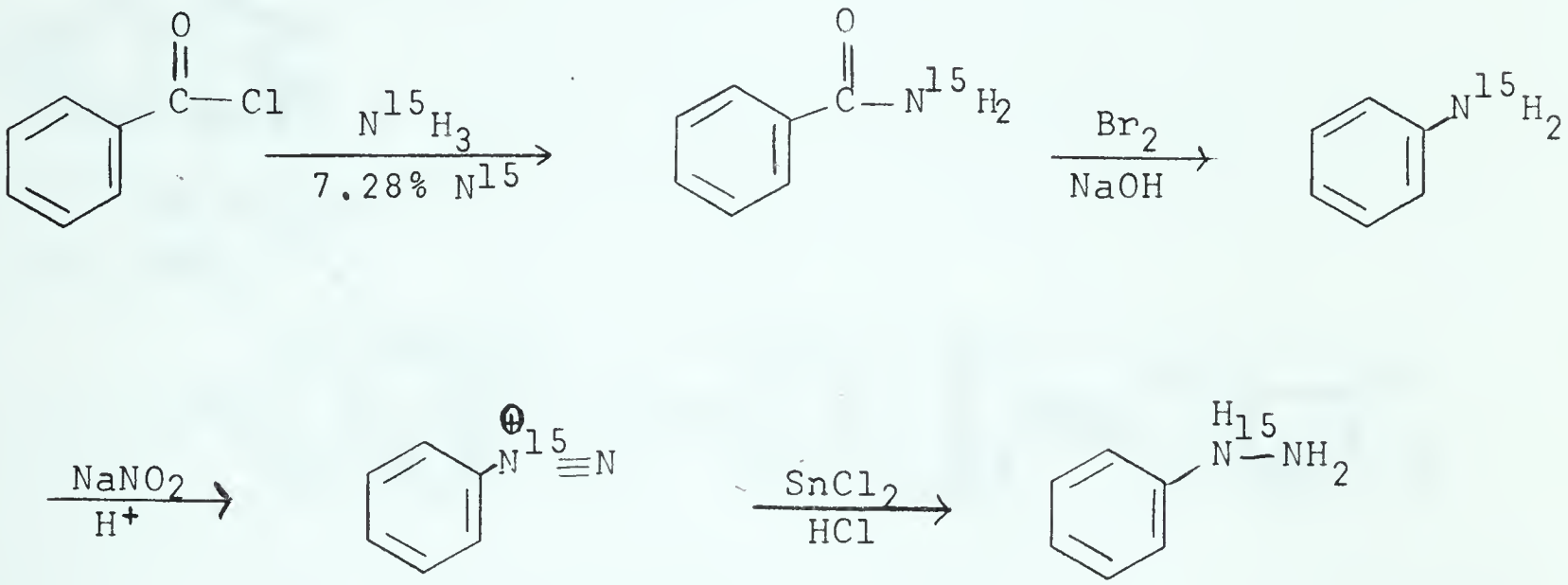


XXII

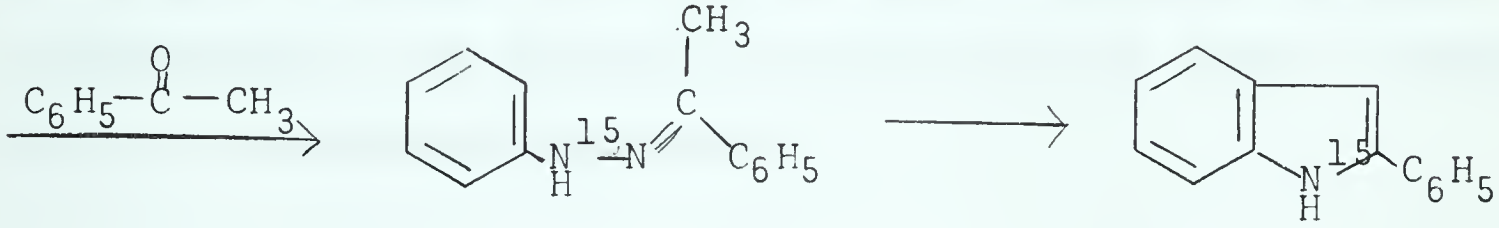
iii. Elimination of Ammonia [step (c)]

Fischer (1, 2, 76), soon after discovering the indole synthesis, considered the question as to which nitrogen of the phenylhydrazone was eliminated as ammonia during cyclization. From the fact that 1-alkyl indoles were obtained from 1-alkyl-arylhydrazones, it was concluded that the 2-nitrogen atom, or the one remote from the aromatic ring, was the one eliminated during ring closure. The first three mechanism proposals for the Fischer reaction failed because they could not adequately account for the formation of 1-alkylindoles. With the advent

of heavy nitrogen Allen and Wilson (49) designed a series of experiments, using N^{15} as tracer, showing that it is indeed the 2-nitrogen atom that is eliminated. They performed the reactions expressed by the following equations.



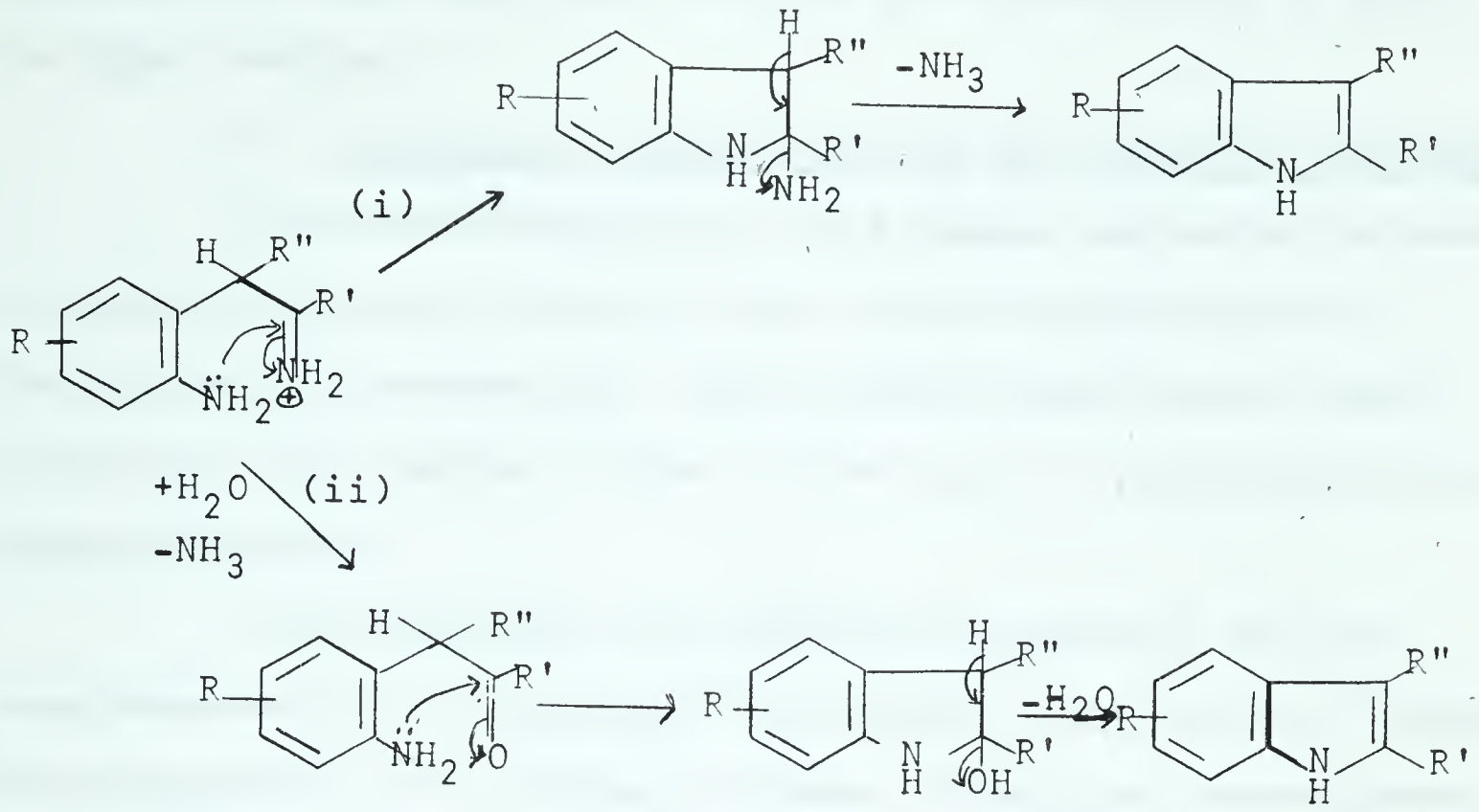
$3.92\pm0.03\%N^{15}$



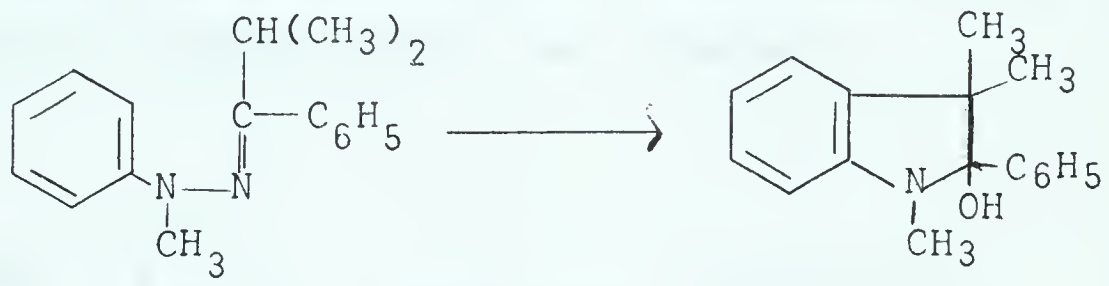
$7.06\pm0.06\%\ N^{15}$

Mass spectrometric analysis showed that the indole did contain all the N^{15}. Clausius and Weisser (77) performed similar experiments with acetone 2-N^{15} phenylhydrazone and showed that the product of the reaction was unlabelled 2-methylindole. This confirmed that the 2-nitrogen atom of the arylhydrazone is the one eliminated during cyclization.

Robinson (39) suggested in 1924 that elimination of the remote nitrogen atom during cyclization might occur by two alternatives schemes. In modern terms, these alternative schemes may be represented by the following equations.



The report by Jenisch (20) that 2-hydroxy-1,3,3,-trimethyl-2-phenylindole was obtained by cyclization of methyl isopropyl ketone 1-methylphenylhydrazone,



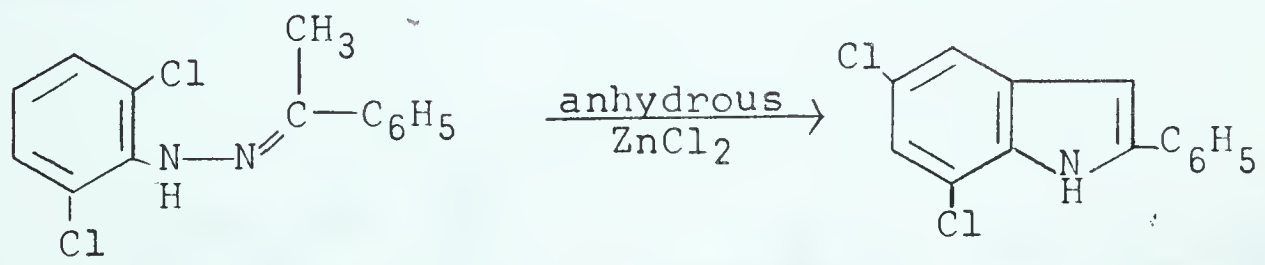
lends support to method (ii), although the possibility of ring closure followed by base attack on the indolium salt must also be considered. Allen and Wilson (49) favored method (i)on the basis of known examples of ketimines that are stable in acid media. In view of the lack of evidence concerning these two alternative

schemes, it seems that this portion of the mechanism is still an open question.

5. Carlin's Interpretation of the Robinson Mechanism

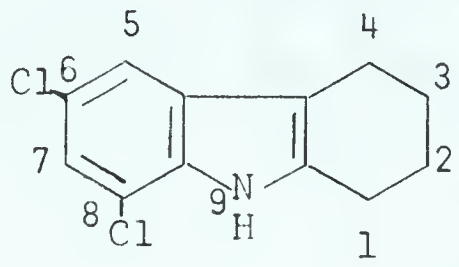
The interpretation of the Robinson mechanism in terms of modern electronic theory is due almost exclusively to Carlin and his co-workers. These workers based their interpretation upon studies on the cyclization of 2,6-disubstituted phenylhydrzones.

From analogies with recorded experiments on the rearrangements of 2,6-disubstituted phenyl allyl ethers (Claisen rearrangement) and of hydrazobenzenes (benzidine rearrangement), Carlin (50) felt that the Fischer cyclization of 2,6-disubstituted phenylhydrazones might take either or both of the following courses: (1) ortho rearrangement, with displacement of a substituent, or (2) para rearrangement. When Carlin (50) heated acetophenone 2,6-dichlorophenylhydrazone with zinc chloride, alone or in the presence of solvents, a low yield of 2-phenyl-5,7-dichloroindole was obtained.



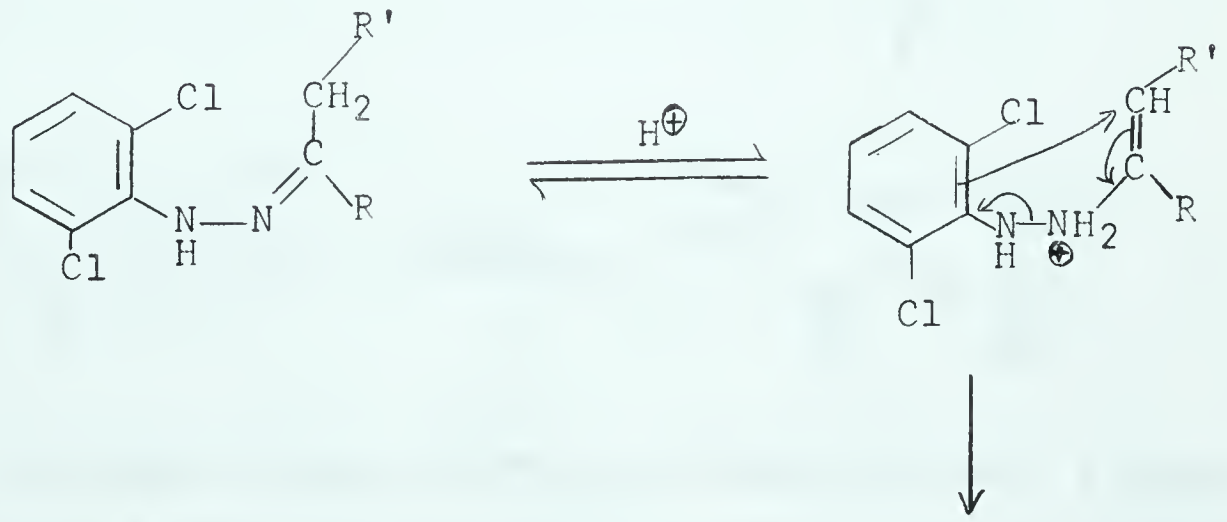
The structure of the product was proven by its hydrogenation to 2-phenylindole and its synthesis from acetophenone 2,4-dichlorophenylhydrazone. Other 2,6-dichlorophenhydrazones behaved

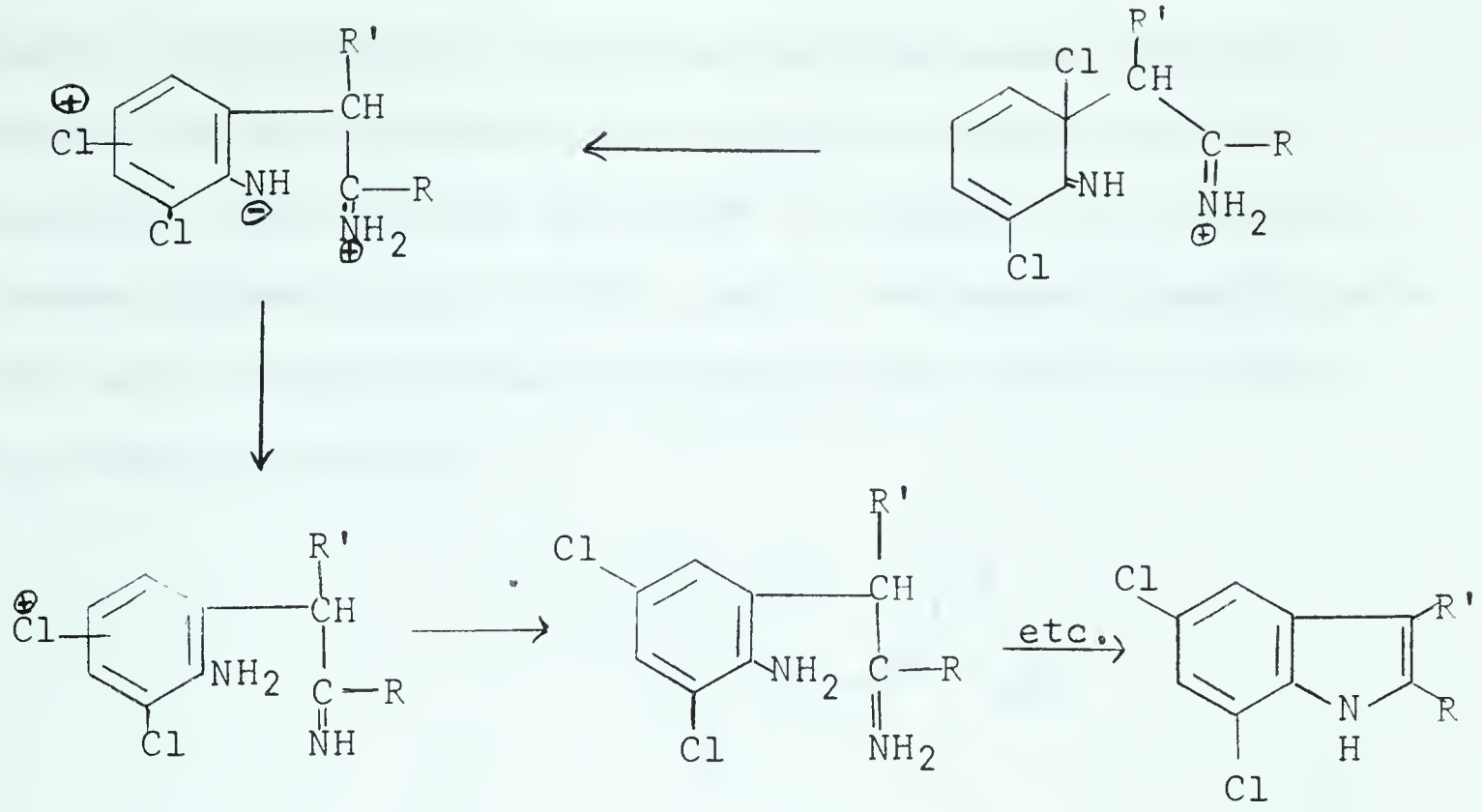
in a similar fashion, and the migration was shown to be specific for these substances since 2,5- and 3,5-dichlorophenylhydrazones were found to give only "normal" cyclization products. Other workers (78) observed a similar migration during the sulfuric acid-catalyzed cyclization of cyclohexanone 2,6-dichlorophenylhydrazone to 6,8-dichloro-1,2,3,4-tetrahydrocarbazole (XXIII).



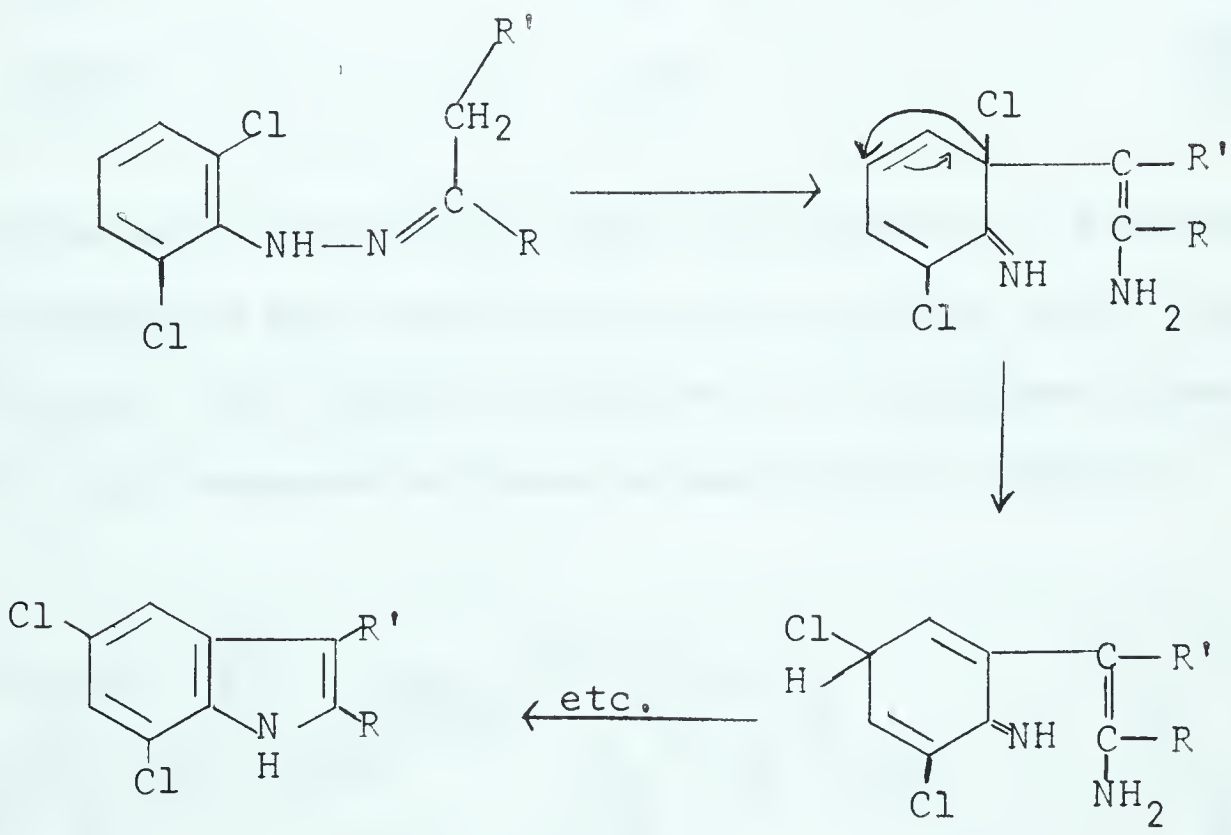
XXIII

Subsequent work by Carlin (79) to determine the nature of migrating chlorine in these reactions suggested that the chlorine migration was intramolecular and that chlorine migrated in an electron deficient or "positive" condition. Carlin summarized these ideas in postulating the following mechanism for the reaction:



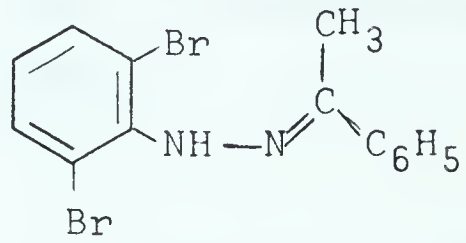


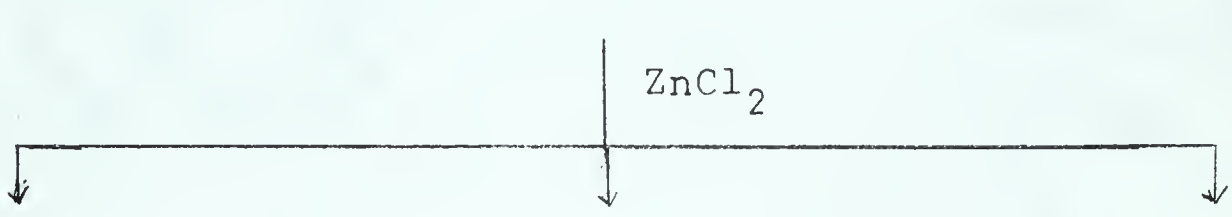
Southwick (79) in a private communication to Carlin, suggested that the experimental observations might also be explained by the following alternative mechanism.

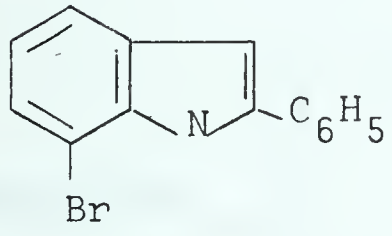


In order to gain further information about Fischer reactions of 2,6-dihalogenated phenylhydrazones, Carlin (80)

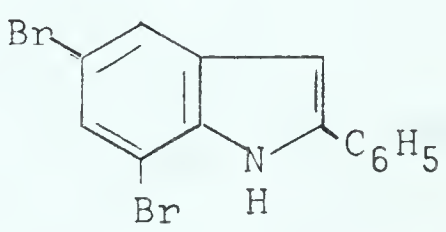
treated acetophenone 2,6-dibromophenylhydrazone with zinc chloride in nitrobenzene and obtained a mixture of three products. This mixture was shown to consist of a trace of 7-bromo-2-phenylindole (XXIV), and 5,7-dibromo-2-phenylindole (XXV) and 7-bromo-5-chloro-2-phenylindole (XXVI) in about equimolar quantities.



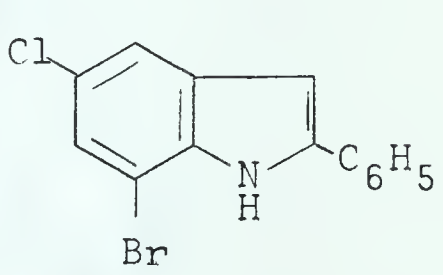




XXIV

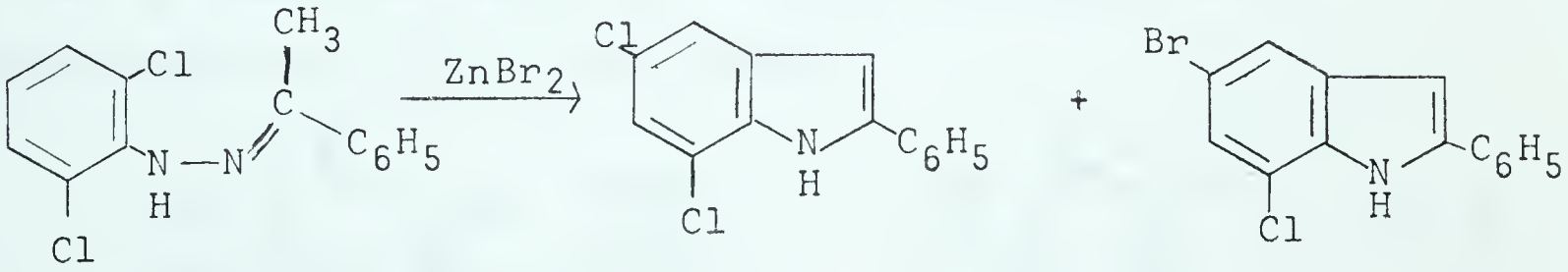


XXV



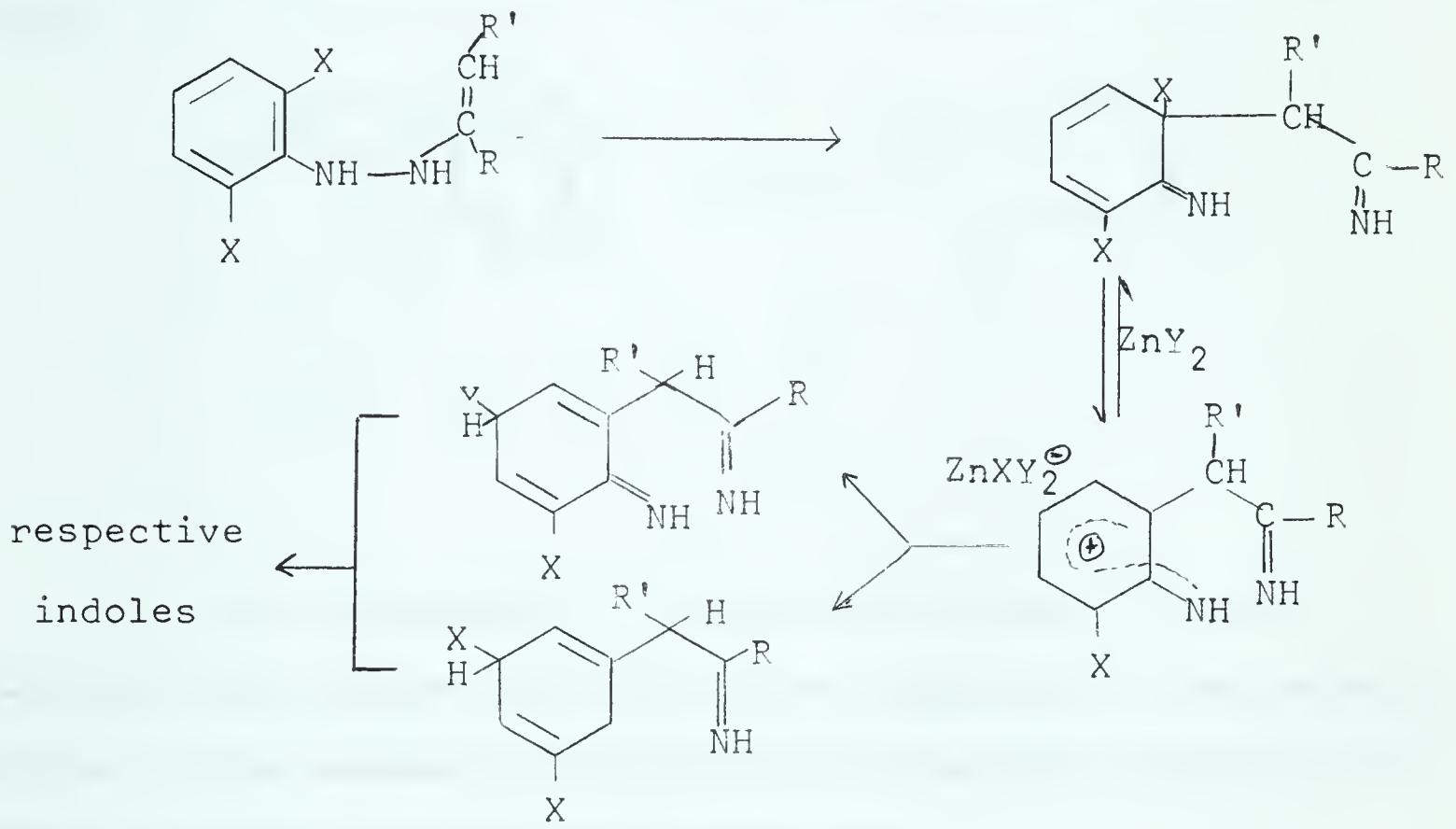
XXVI

A mixture was also obtained when acetophenone 2,6-dichlorophenylhydrazone was treated with zinc bromide under similar conditions. This mixture contained 5,7-dichloro-2-phenylindole (XXVII) and 5-bromo-7-chloro-2-phenylindole (XXVIII).



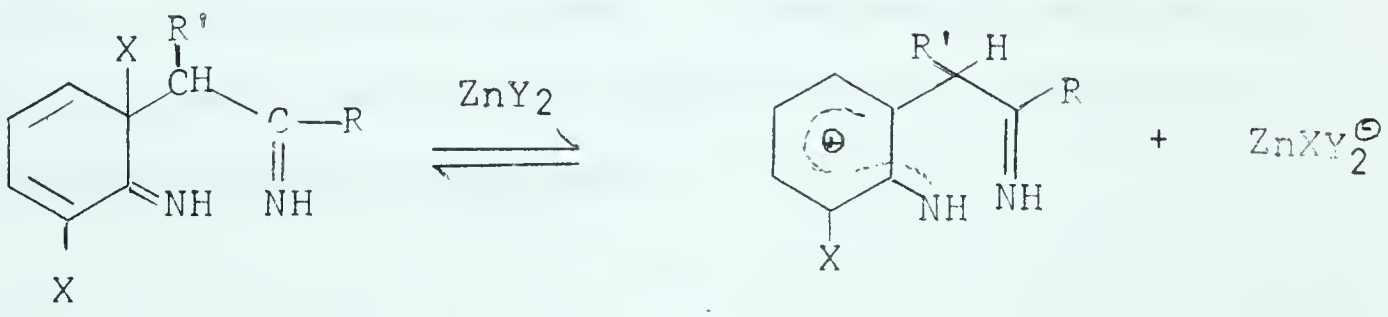
XXVII XXVIII

In addition to halogen migration, the foregoing results indicated that halogen exchange and replacement of halogen by hydrogen were also possible. Upon considering the relative oxidation potentials of the two halogen-halide systems, Carlin decided that exchange between $Br^{\oplus}$ and $ZnCl_2$ was unlikely and revised his "positive" halogen mechanism accordingly. To account for the new observations, the revised mechanism was written as follows:

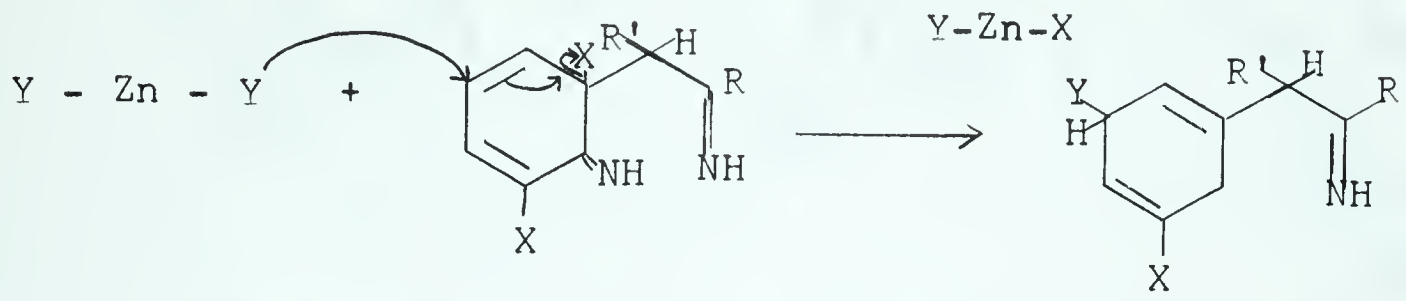


However, Carlin (80) suggested three other possible mechanisms that adequately explain the observed migrations and exchanges. These were:

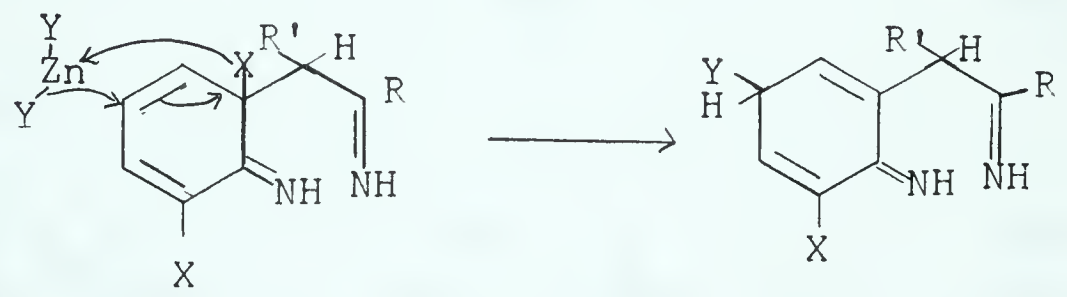
(a) An S_N1 reaction, which is the above mechanism with greater separation of the ions formed.



(b) An S_N2' transformation such as illustrated below.

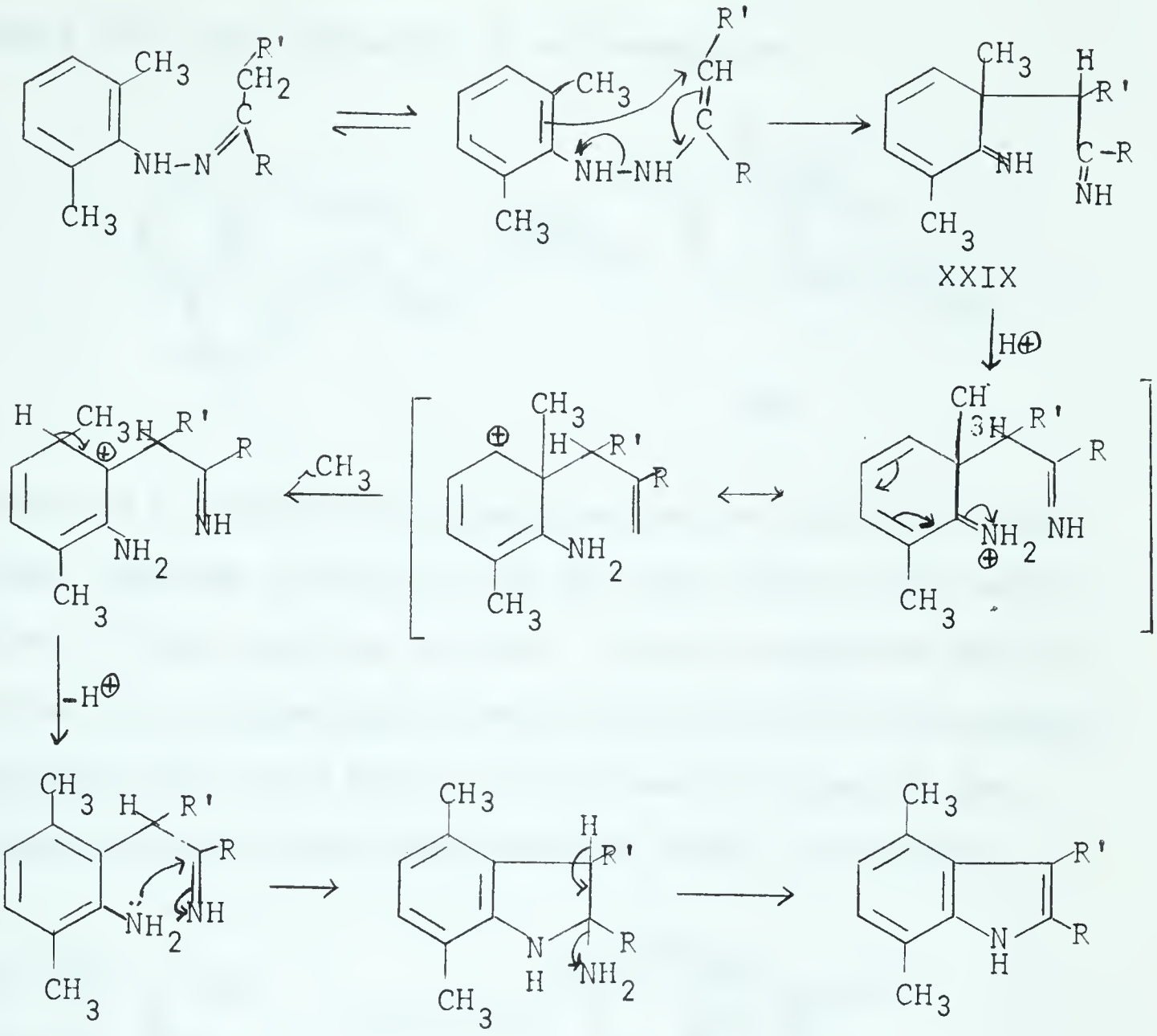


(c) A concerted reaction involving a 6-membered transition state.



The replacement of halogen by hydrogen to yield 7-halogenated indoles (80, 81) can be explained by the reducing action of the reagent, with any proton-donating species in the reaction mixture supplying the hydrogen.

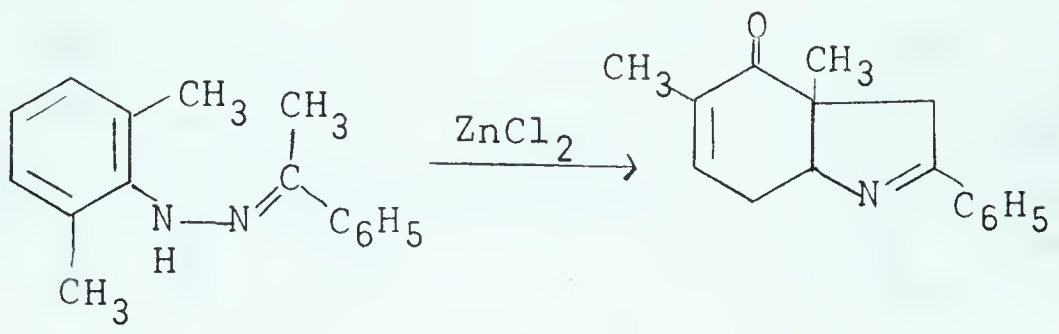
In further studies on 2,6-disubstituted phenylhydrazones, Carlin found (82) that migrations also occurred when 2,6-dimethylphenylhydrazones were cyclized under Fischer conditions. However, the migrating methyl groups was shown to end up in the 4-position of the indole formed. A mechanism, similar to that used to explain the halogen migrations, was proposed to account for these methyl migrations.



XXIX

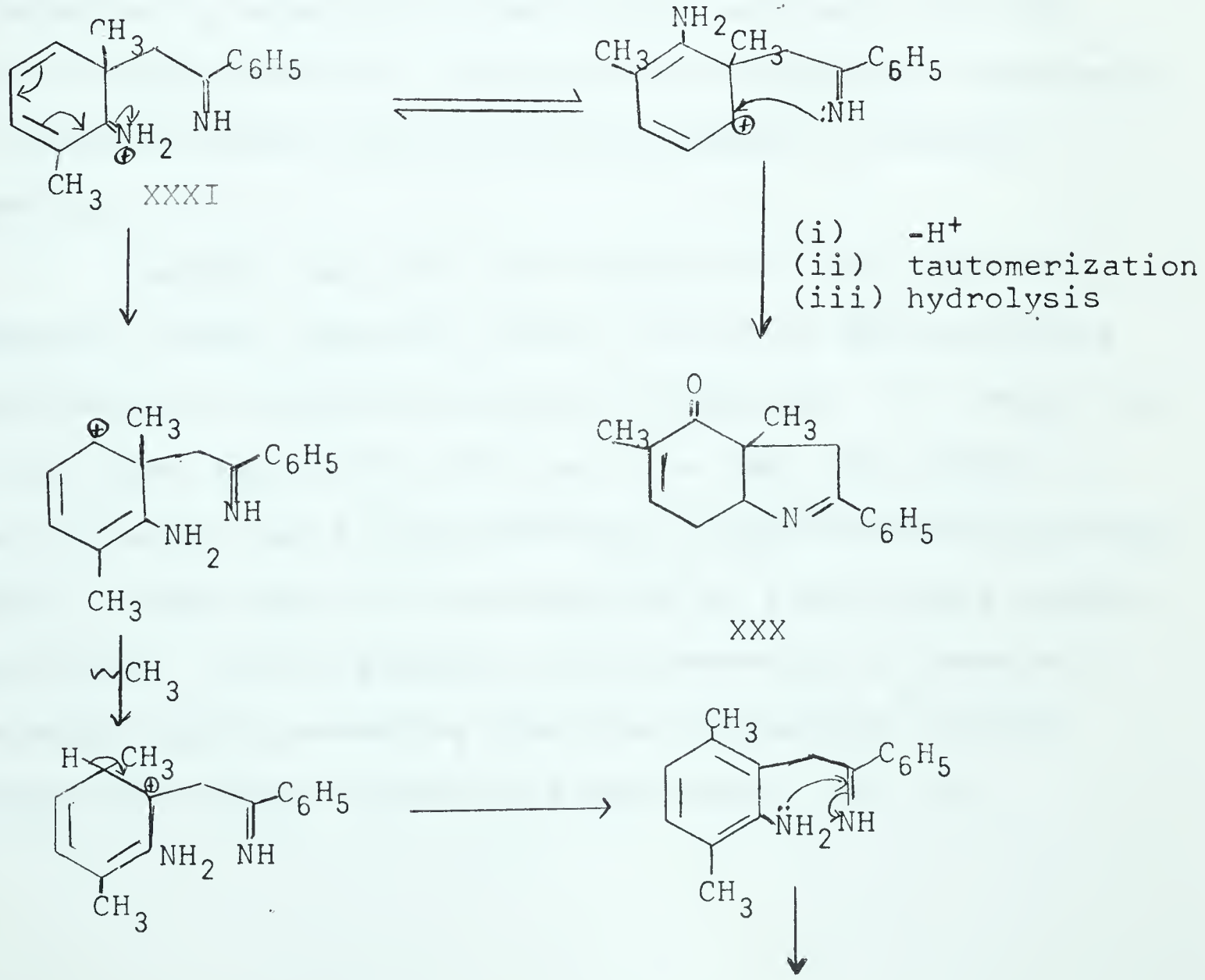
In addition to interpreting Robinson's mechanism in modern electronic terms, Carlin has also included dienone-imine intermediates like XXIX as an essential feature in all of his mechanism proposals. In order to gain evidence in support of these intermediates, Carlin attempted (82) to trap XXIX as a maleic anhydride Diels-Alder adduct. These attempts failed, however. Carlin suggested (82) that these failures might have been due to the rapid conversion of XXIX into succeeding intermediates. Some evidence for the dienone-imine intermediate XXIX was obtained when a non-aromatic intermediate XXX was isolated upon cyclization of acetophenone 2,6-dimethylphenyl-

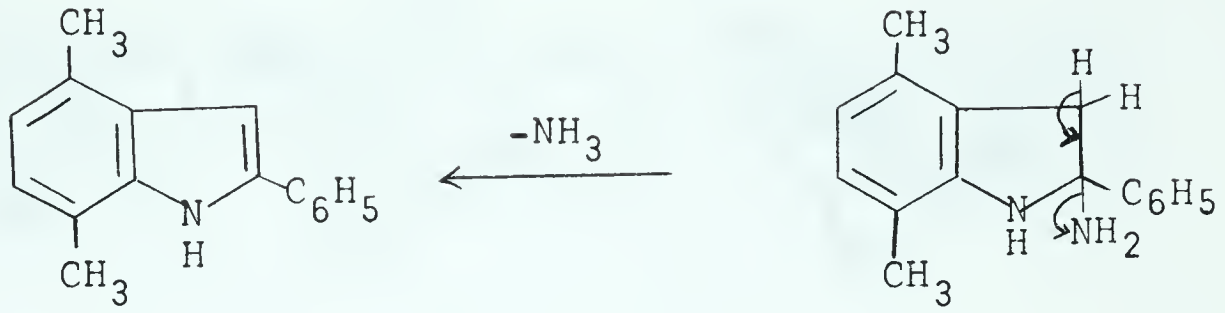
hydrazone with zinc chloride in nitrobenzene.



XXX

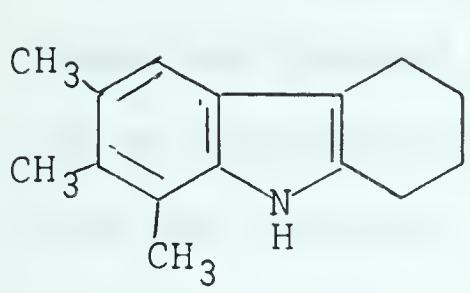
The expected 4,7-dimethyl-2-phenylindole was isolated along with some cleavage products, but the base XXX was the major component of the reaction mixture. Carlin suggested that the formation of 4,7-dimethyl-2-phenylindole and the non-aromatic intermediate XXX could best be explained in terms of the postulated dienone-imine intermediate (XXXI) as follows:



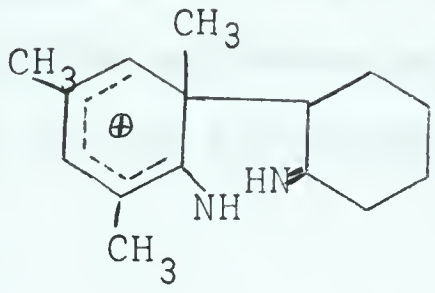


The proposed mechanisms for the formation of 4,7-dimethyl-2-phenylindole and XXX require that the 1-nitrogen of the arylhydrazone (that attached to the aromatic ring) be retained in 4,7-dimethyl-2-phenylindole and lost from XXX. Carlin has indicated his intentions (84) to perform experiments to determine whether this predicted behavior is actually observed.

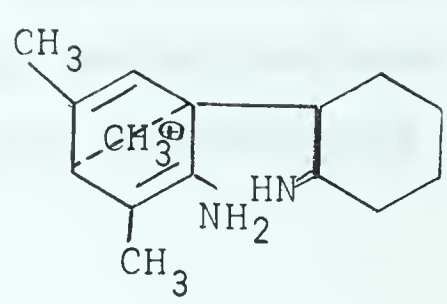
Barnes, Pausacker, and Badcock (87) had previously observed a methyl migration during the acetic acid-catalyzed cyclization of cyclohexanone mesitylhydrazone. In a repetition of this work, Carlin (85, 86) has shown that the product of the cyclization was 6,7,8-trimethyl-1,2,3,4-tetrahydrocarbazole (XXXII), rather than an "isocarbazole" as the previous authors had claimed. Carlin explained this conversion in terms of a 1,4-methyl shift proceeding from the intermediate (XXXIII) through the bridged transition state (XXXIV) (85, 86).



XXXII



XXXIII

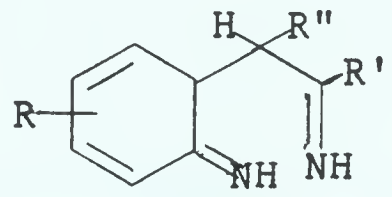


XXXIV

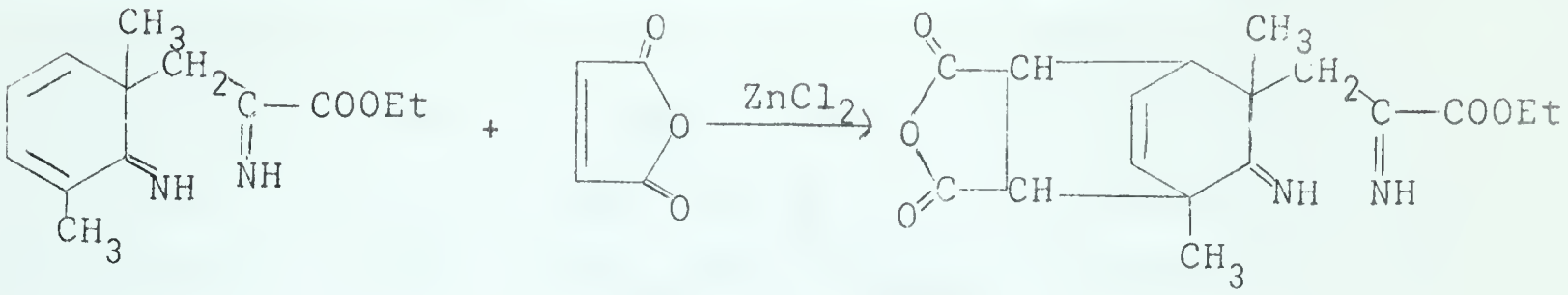
The foregoing summarizes the essential features of recorded work on the Fischer indole synthesis, and it is upon this background information that the present study is based.

II Results and Discussion

Carlin suggested (79-86) that all of his products from the Fischer indole synthesis might be rationalized if an intermediate of the following type is postulated for the reaction:



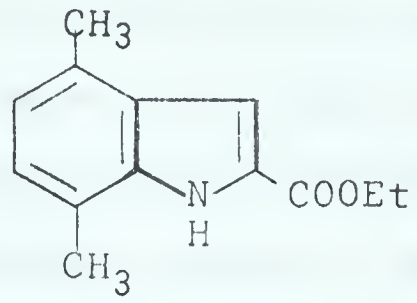
He drew the analogy between this intermediate and the dienone intermediate in the Claisen rearrangement. The dienone intermediate in the Claisen rearrangement had been "trapped" in a Diels-Alder reaction by Conroy and Firestone (88, 89) and synthesized by Curtin and Crawford (90). Carlin suggested (82) that the dienone-imine intermediate in the Fischer indole synthesis might also be "trapped" by maleic anhydride to form a Diels-Alder adduct similar to that isolated by Conroy and Firestone (88, 89). To that end, he heated ethyl pyruvate 2,6-dimethylphenylhydrazone with excess maleic anhydride and a large excess zinc chloride, both in the presence and in the absence of solvent nitrobenzene, in an attempt to promote the following reaction:



XXXV

Small quantities of amorphous or semi-crystalline materials having acidic properties were isolated after steam distillation of several of the reaction mixtures, but only one of these yielded a pure crystalline solid. This yellow solid, m.p. 110 - 111°, of which only 10 mg. was obtained in pure form by high vacuum sublimation, gave analytical values corresponding to the formula $C_{12}H_{14}N_2O_3$ and showed an ultraviolet spectrum with one maximium at about 245 mμ and another, much more intense, well above 320 mμ. A maleic anhydride adduct (to XXXV) would have the formula $C_{17}H_{21}N_2O_5$ in the unlikely event that the nitrogen linkages could survive hydrolysis during steam distillation. Furthermore, no normal adduct would be expected to yield an ultraviolet spectrum such as the one observed. [Conroy and Firestone (89) found no high intensity absorption, but did find the characteristically weak ketone band at 303 mμ (ε64) for their adduct]. Apparently, then, no substance corresponding to an addition product of maleic anhydride and the dienone-imine intermediate (XXXV) was isolated. However, a small amount of the indole

(XXXVI) was obtained, showing that at least some cyclization was occurring under the reaction conditions employed.



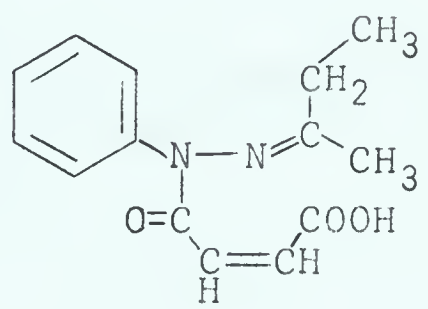
XXXVI

Since the appearance of the paper describing this work (82), Carlin has reported no further attempts at "trapping" the postulated dienone-imine intermediate.

A. Experiments Involving the Cyclization of Methyl Ethyl Ketone Phenylhydrazone.

Our first approach to the problem of obtaining evidence in support of the dienone-imine intermediate proposed by Carlin (79 - 86) was also aimed at attempting to "trap" the intermediate in a Diels-Alder reaction. In our opinion the experimental conditions used by Carlin (83) (a 3-fold of excess $ZnCl_2$ and 135°) were much too strenuous for formation of a Diels-Alder adduct. It was necessary then to find an easily cyclized phenylhydrazone for our study. Pertinant to this work is the discovery by Fitzpatrick and Hiser (71) that a catalyst is unnecessary in the Fischer reaction and that a list of ten different indoles can be formed by refluxing the corresponding phenylhydrazones in

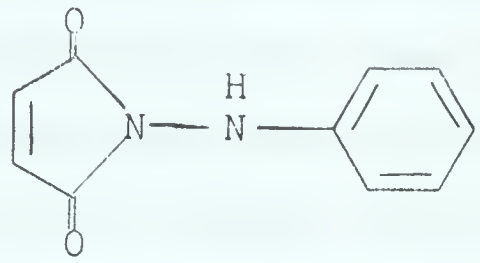
a suitable solvent. Methyl ethyl ketone phenylhydrazone seemed particularly suited to study because of its ease of transformation to 2,3-dimethylindole. For example, in a trial run, refluxing methyl ethyl ketone phenylhydrazone in tetralin for 3 hours gave a 42% yield of 2,3-dimethylindole. Consequently, methyl ethyl ketone phenylhydrazone was heated in tetralin with a five-molar excess of maleic anhydride and a solid, base-soluble product was obtained, melting at 261 - 262°. No 2,3-dimethylindole was obtained. The infrared spectrum showed that the compound was not the expected adduct since the bands at 1865 and 1782 cm^{-1}, characteristic of succinic anhydrides (91), were absent. There was, however, a band at 1685 cm^{-1} due to $-\overset{O}{\overset{\|}{C}}-N-$ (92). On the basis of this infrared band and la Parola's claim (93) that the only reaction between maleic anhydride and phenylhydrazones is that of amide formation, the 261-262° melting material was tentatively assigned the structure (XXXVII).



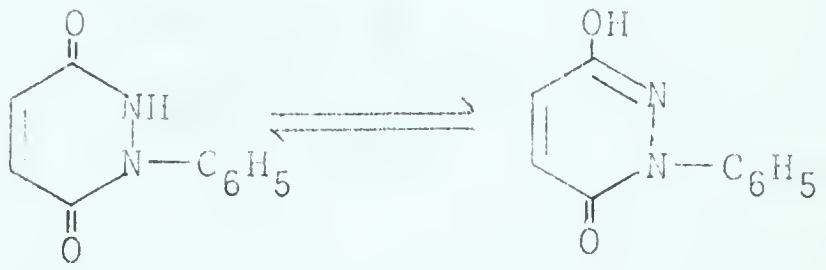
XXXVII

However, a molecular weight determination and elemental analysis showed the compound to have the composition

$C_{10}H_8N_2O_2$. The amide (XXXVII)would have the composition $C_{14}H_{16}N_2O_3$. A search of the literature showed that Jolles (94) and Druey and co-workers (95) had treated maleic anhydride with phenylhydrazine to obtain maleinyl phenylhydrazide of empirical formula, $C_{10}H_8N_2O_2$, m.p. 260°. Jolles (94) had assigned the following structure to this hydrazide.



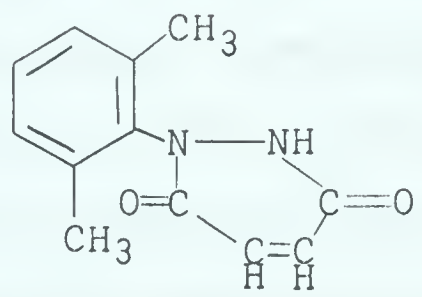
However, this structure does not agree with the observed base solubility of the compound obtained. Druey and co-workers (95) showed the correct structure to be:



Such a structure does account for the base solubility.

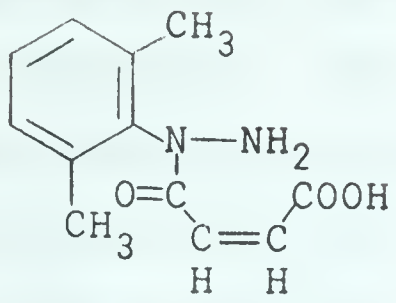
Preparation of an authentic sample of maleinyl phenylhydrazide for comparison with our compound by infrared

and mixture melting point deteriminations showed that our compound was indeed maleinyl phenylhydrazide. The hydrazide was very readily formed since by mixing equimolar quantities of maleic anhydride and methyl ethyl ketone phenylhydrazone at 70° we obtained maleinyl phenylhydrazide as the only condensation product. In no case was the amide (XXXVII) (93) obtained. Again, no 2,3-dimethylindole was obtained. It appears that hydrazide formation takes precedence, with the ketone portion of the hydrazone being removed during reaction. On reflection, it seemed likely that this would explain Carlin's failure (83) to obtain the Diels-Alder adduct. Carlin's compound possessed the empirical formula $C_{12}H_{14}N_2O_3$. A hydrazide from Carlin's hydrazone and maleic anhydride would have the formula $C_{12}H_{12}N_2O_2$ and the structure (XXXVIII).

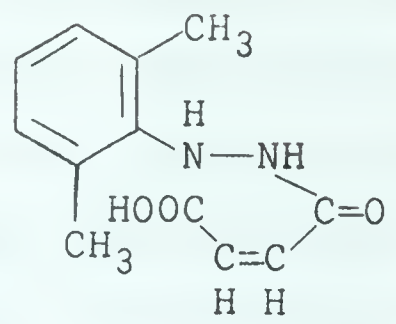


XXXVIII

Thus, Carlin's base soluble product corresponds to an hydrolysis product of the hydrazide (XXXVIII) and could be either of the amides shown below.



or



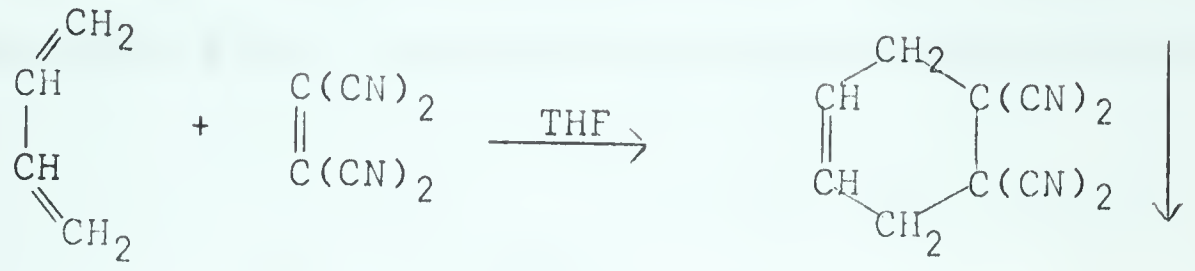
Hydrolysis of the hydrazide to one of the amides shown above could easily have occurred during the steam distillation used in the work-up of his reaction mixture.

Thus it appeared that for the successful "trapping" of the proposed dienone-imine intermediate, it would be necessary either to study a phenylhydrazone which does not react with maleic anhydride to form hydrazides or find a suitable dienophile which does not react at the nitrogen atoms of methyl ethyl ketone phenylhydrazone. It seemed likely that replacement of the active hydrogen on the nitrogen of methyl ethyl ketone phenylhydrazone might decrease or eliminate the undesirable reaction with maleic anhydride. Thus,methyl ethyl ketone N-methylphenylhydrazone would meet the first of these requirements. Consequently, methyl ethyl ketone N-methylphenylhydrazone was prepared and refluxed in tetralin. A fair yield (63%) of 1,2,3-trimethylindole was obtained upon reduced pressure distillation of the reaction mixture. This showed that cyclization does occur under these conditions and therefore we may assume the presence of the

proposed dienone-imine intermediate in the reaction mixture. The experiment was then repeated in the presence of excess maleic anhydride. Upon reduced pressure distillation of this reaction mixture, approximately the same yield of 1,2,3-trimethylindole (66%) was obtained. Upon acidification of the basic extract from the residue of this distillation, only unreacted maleic anhydride could be isolated. However, this is no clear indication that the adduct is not formed. It is known that the Diels-Alder reaction is reversible and that high temperatures tend to favor decomposition of the adduct to the original reactants (96). This difficulty is usually avoided by using a very large excess of maleic anhydride (as much as 30 moles per mole of diene) (97). When one considers the yield of 1,2,3-trimethylindole obtained in the presence of maleic anhydride, as well as the low yield (6.3%) of adduct obtained by Conroy and Firestone (89), it is realized that only a small quantity of adduct would be expected and its presence might very well be obscured by the large quantity of maleic anhydride used. In view of this, this line of attack was abandoned in favor of finding a more suitable dienophile.

Cairns and co-workers (98) had recently reported the preparation of tetracyanoethylene and further work by Middleton (99) had shown that this compound was an unusally active dienophile. For example, when butadiene is bubbled into a cold solution of tetracyanoethylene in tetrahydrofuran, the adduct 4,4,5,5,-tetracyano-1-cyclohexene (XXXIX) precipitates from the solution almost instantaneously

in nearly quantitative yield.

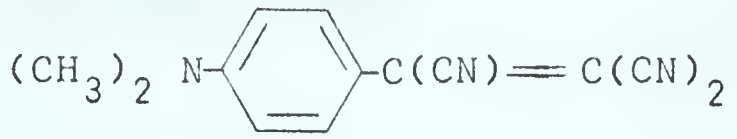


XXXIX

Thus, it seemed that tetracycanoethylene might be a suitable dienophile for "trapping" the dienone-imine intermediate. To this end, equimolar quantities of methyl ethyl ketone phenylhydrazone and tetracyanoethylene (100) were refluxed in tetralin for one hour. Upon removal of most of the tetralin from the dark solution by reduced pressure distillation, a black finely-divided solid precipitated, m. p. $>300°$. Further reduction in volume of the tetralin solution produced more of this black solid upon cooling. Attempts at recrystallization and decolorization were of no avail. It was thought that the product was probably a result of polymerization of tetracyanoethylene and no further attempts at characterization were made. A further search of the literature revealed (101) that tetracyanoethylene reacts with primary and some secondary amines to give N-tricyanovinylamines as illustrated below.

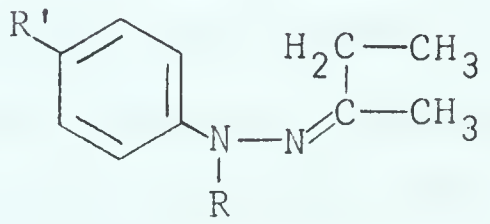
$$RR'NH + C(CN)_2{=}C(CN)_2 \longrightarrow RR'NC(CN){=}C(CN)_2 + HCN$$

It is known also that tetracyanoethylene readily reacts with both tertiary and secondary aromatic amines, attacking the ring to give 4-tricyanovinylamines. For example, N,N-dimethylaniline gives 4-tricyanovinyl-N,N-dimethylaniline (XL) (101).



XL

Thus is would seem that for the successful use of tetracyanoethylene as a "trapping agent", even if no polymerization occurred, it would be necessary to design a hydrazone with blocking groups on the nitrogen and in the para-position of the ring (XLI). Because of this, as well as the polymeriza-

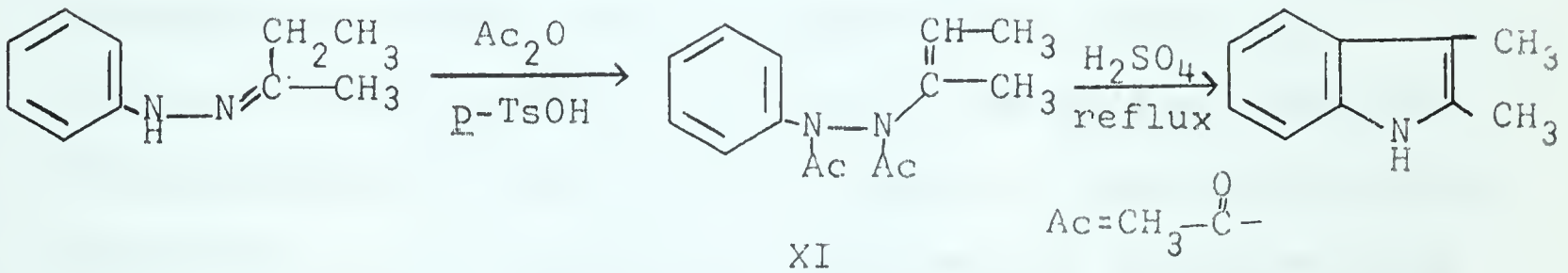


XLI

tion of tetracyanoethylene under conditions known to produce the indole, the use of tetracyanoethylene was not pursued any further.

B. Experiments Involving the Cyclization of the Diacetyl Derivative of Methyl Ethyl Ketone Phenylhydrazone.

Suvorov and co-workers (62) recently were successful in preparing the diacetyl derivative of methyl ethyl ketone phenylhydrazone (XI) and cyclized this compound according to the following scheme:

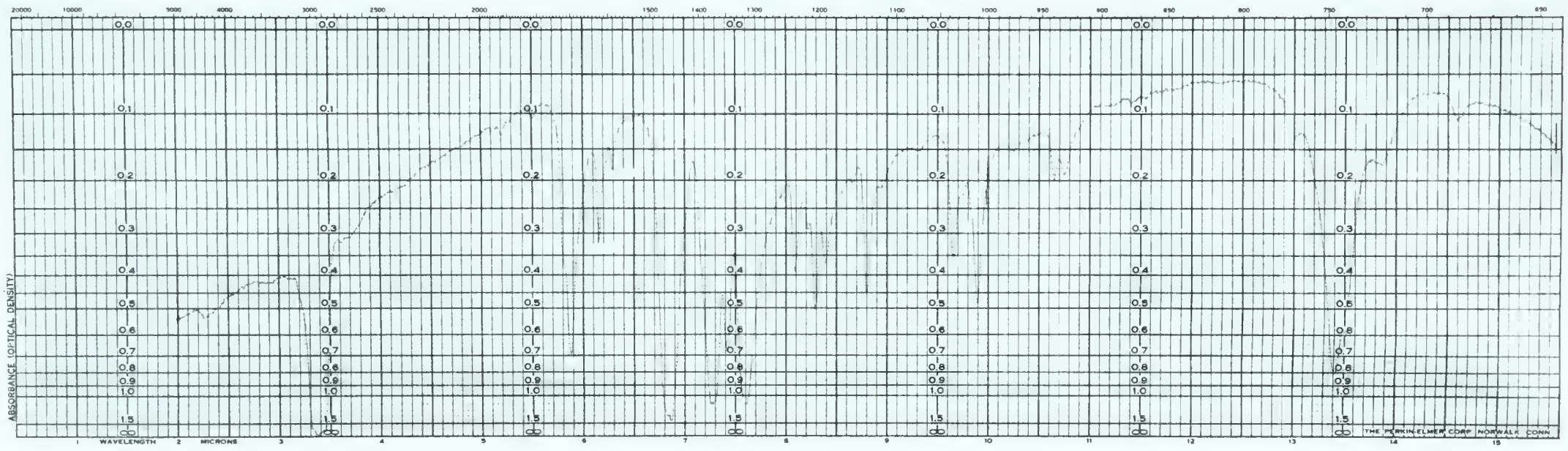


XI

The diacetyl compound (XI) seemed particularly suited to our use, not only because the presence of the acetyl groups would prevent hydrazide formation (though there is perhaps some possibility of amide exchange), but also because the diacetyl compound is in the enehydrazine form of the hydrazone and thus is one step further toward the product indole. However, the conditions of cyclization employed by these workers were not suitable for use with the dienophile we had chosen, since refluxing mineral acid would result in hydrolysis of maleic anhydride. Consequently, we prepared the diacetyl compound (XI) by Suvorov's procedure (62) and attempted its cyclization in refluxing benzene (to avoid

hydrolysis of the maleic anhydride) with catalytic amounts of p-toluenesulfonic acid. When the reaction mixture was washed with dilute sodium hydroxide to remove p-toluenesulfonic acid and the benzene evaporated, a 41% yield of 2,3-dimethylindole, m. p. 103-105°, was obtained. This indicated that our conditions were sufficient to produce cyclization. When this experiment was repeated without the base wash, a compound of melting point 65-67° was obtained. Recrystallization raised this melting point to 71-72°. Infrared bands were present at 1700(-C(=O)-N-), 1620, and 1590 cm^{-1} (both aromatic C=C) but no -NH band was observed. This spectrum is illustrated in Figure 1. Repetition of the experiment in the presence of excess maleic anhydride using a base wash of the benzene solution to remove unreacted maleic anhydride, p-toluenesulfonic acid and any adduct which might have been formed, produced the same 71-72° melting material, as shown by infrared and mixture melting point determinations. Only unreacted maleic anhydride was isolated upon acidification of the aqueous layer. Refluxing the 71-72° melting material in benzene with p-toluenesulfonic acid produced the characteristic odor of 2,3-dimethylindole and the melting point of the crude product obtained was depressed, giving a melting point of 65-68°. The infrared spectrum of this crude material did not, however, show the -NH band due to the pyrrole ring of the indole nucleus. Thus, the amount of 2,3-dimethylindole present must be extremely small and thus escapes detection by the spectrophotometer. Elemental analysis of the 71-72° melting material showed it to have the empirical

Figure 1



I. R. Spectrum of 1-Acetyl-2,3-dimethylindole in Nujol.

formula, $C_{12}H_{13}NO$. Further examination of the 71-72° melting material showed it to be 1-acetyl-2,3-dimethylindole. An authentic sample (102) of 1-acetyl-2,3-dimethylindole gave an infrared spectrum identical to that of the 71-72° melting material and a mixture melting point showed no depression. The infrared spectrum of authentic 1-acetyl-2,3-dimethylindole is shown in Figure 2. Thus, the only detectable reaction occurring was that of cyclization of the diacetyl compound (XI) to the corresponding indole and no information concerning the dienone-imine intermediate was obtained from this series of experiments.

Next, an attempt was made to cyclize the diacetyl compound (XI) by refluxing in spectro grade carbon tetrachloride without a catalyst. Aliquots were taken at two-hour intervals and infrared spectra run to see if any spectral evidence for the dienone-imine intermediate could be obtained. Even after having been heated in refluxing carbon tetrachloride for 24 hrs., the diacetyl compound was quite unchanged and gave the same spectrum as that of the starting compound (XI). Thus, no cyclization to the indole occurred under these conditions.

At this point it was thought that heating the diacetyl derivative (XI) in molten excess maleic anhydride in the absence of a solvent might prove fruitful. The higher temperature should favor more cyclization and the high concentration of maleic anhydride should make the chances of "trapping" the postulated dienone-omine intermediate greater. When such an experiment was carried out in a sublimation

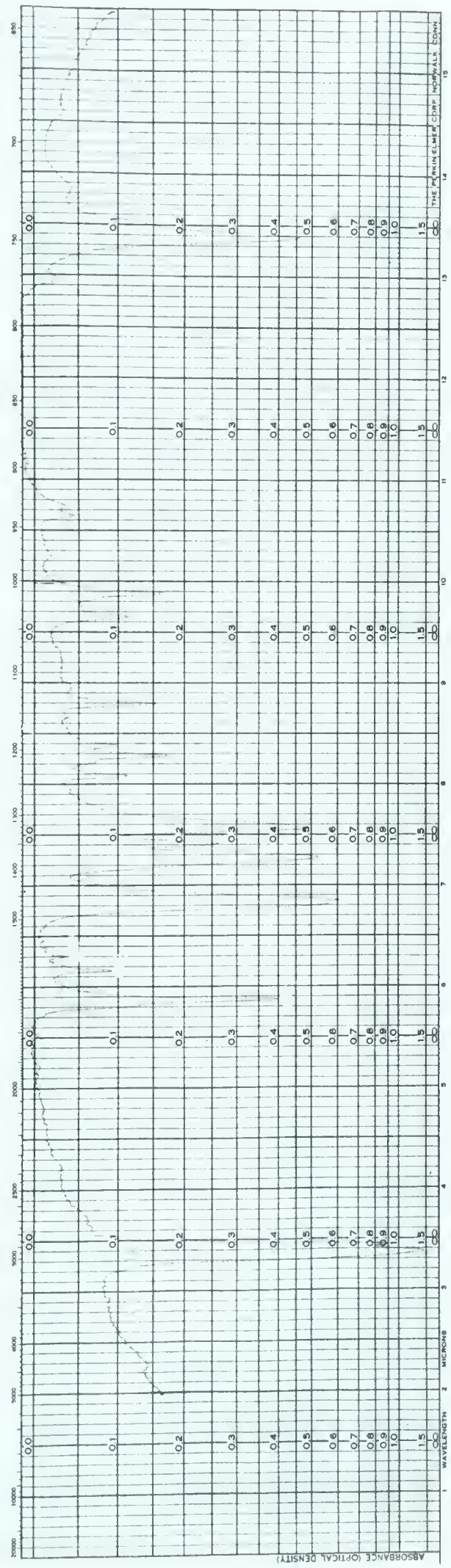
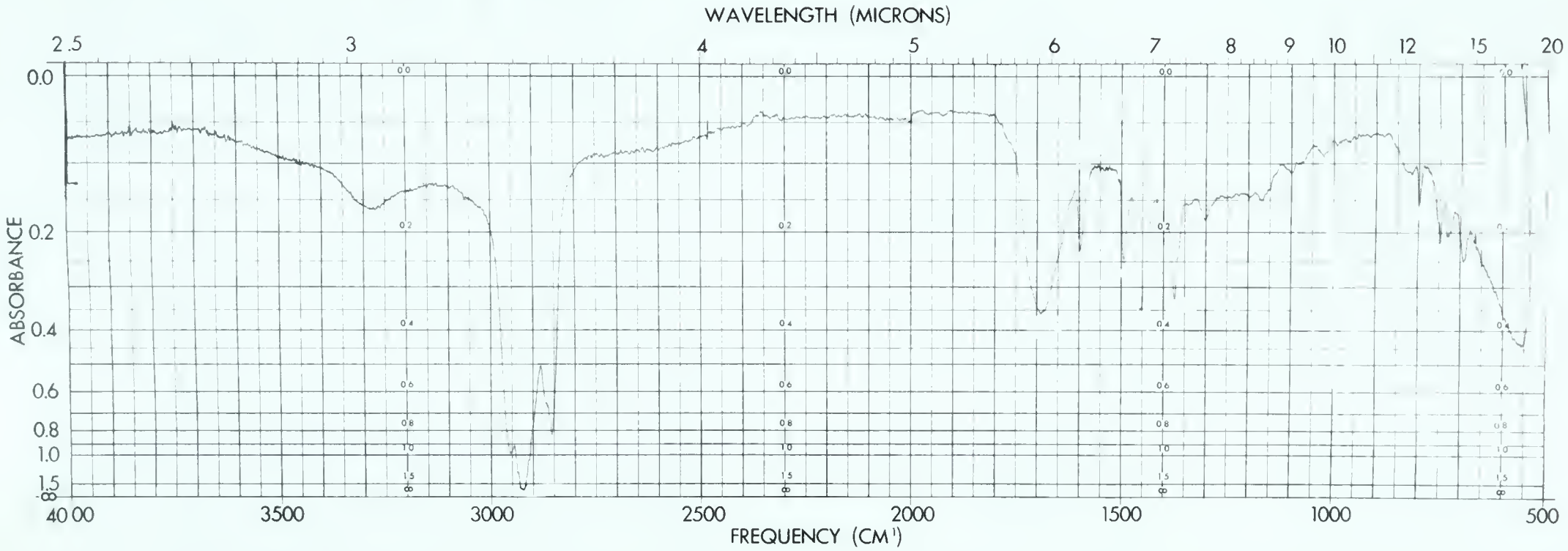


Figure 2

I. R. Spectrum of Authentic 1-Acetyl-2,3-dimethylindole in Nujol.

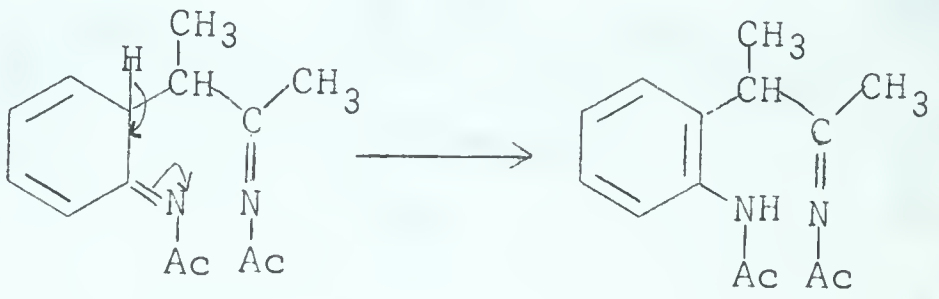
apparatus at 150° for one hour, a large quantity of maleic anhydride sublimed. The discolored residue was stirred with cold, aqueous sodium hydroxide to dissolve any adduct which might have formed as well as unreacted maleic anhydride. The basic solution was acidified to pH 5.5-6.0 and extracted with ether in a continuous liquid-liquid extractor. Evaporation of the dried ether extract yielded a small amount (30 mg.) of a substance, m. p. 98 - 100°. The infrared spectrum of this substance showed a broad, weak band centered at about 3280 cm^{-1}, a strong band at 1690 cm^{-1}, and a band of medium intensity at 1600 cm^{-1}. The 3280 and 1690 cm^{-1} bands were thought to be due to the -COOH grouping and the 1600 cm^{-1} band to aromatic C=C. This spectrum is shown in Figure 3. The substance behaved like a carboxylic acid, being soluble in base and reprecipitated by acid. The infrared spectrum, however, did not possess bands which could be ascribed to C=N (1650 - 1680 cm^{-1} (103) or aliphatic C=C (1620 - 1680 cm^{-1}) (104). Even if the C=N linkages did not survive treatment with base, ketonic carbonyl and aliphatic C=C bands would be expected. Also, acidification of the carboxylate anions of rigid or highly substituted succinic acids usually causes spontaneous cyclization back to the anhydride forms, as was the case with the adducts obtained by Conroy and Firestone (88, 89). Thus, the substance displayed none of the infrared spectral features expected of the Diels-Alder adduct of the postulated dienone-imine intermediate and no further attempt at its characterization was made. Crystallization of the base-insoluble residue

Figure 3



I. R. Spectrum (in Nujol) of Acidic Material from Peaction of Molten Maleic Anhydride with the Diacetyl Derivative of Methyl Ethyl Ketone Phenylhydrazone.

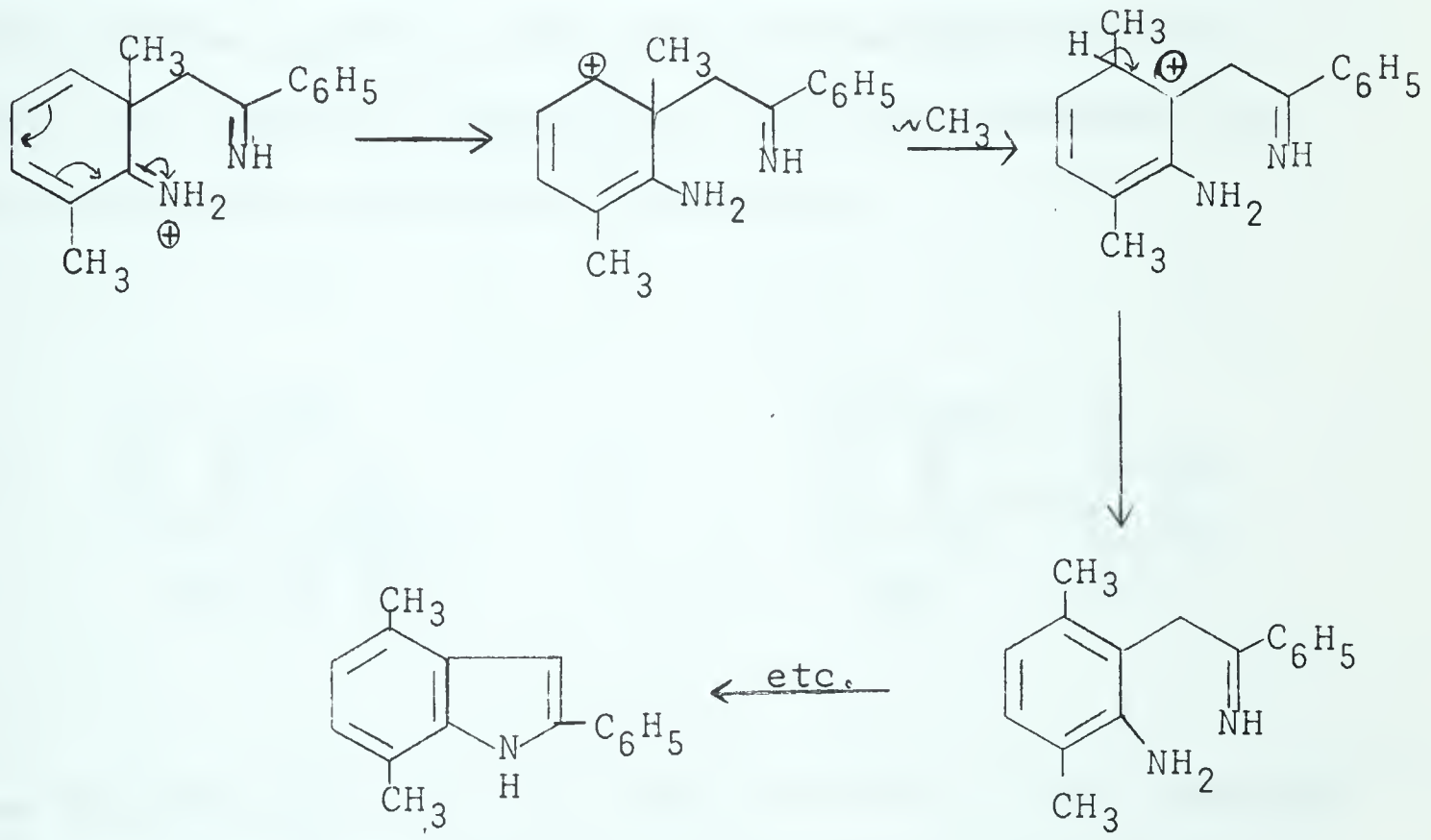
from the reaction gave a 52% yield of 1-acetyl-2,3-dimethyl-indole. Even though considerable cyclization occurred, no Diels-Alder reaction between maleic anhydride and the postulated dienone-imine intermediate occurred to a detectable extent. The success of this Diels-Alder reaction would depend upon its being comparable kinetically to the aromatization of the postulated dienone-imine intermediate,



Although there is no kinetic data available to compare the two reactions, it would appear from the foregoing experiments that the aromatization of the dienone-imine intermediate is very fast as compared to the desired Diels-Alder reaction or that if the adduct did form it was by a reversible reaction which then gave the original dienone-imine which aromatized irreversibly. Thus the Diels-Alder reaction might have more chance of success if some method could be found of slowing the aromatization of the dienone-imine intermediate.

C. Acetylation of 2,6-Dimethylphenylhydrazones

It seemed that one possibility of slowing the aromatization of the dienone-imine intermediate would be by use of methyl groups in the 2- and 6- positions of the phenylhydrazone, since Carlin's products (83) indicated that it was necessary for a methyl migration to occur before aromatization could take place, as shown below.



Here again, we wished to avoid the possibility of hydrazide formation and obtain the enehydrazine form of the hydrazone by acetylation of the nitrogen atoms. Thus, we attempted the preparation of the diacetyl derivative of methyl ethyl ketone 2,6-dimethylphenylhydrazone by refluxing the hydrazone in

excess acetic anhydride in the presence of p-toluenesulfonic acid. Neutralization of the p-toluenesulfonic acid with sodium acetate, followed by reduced pressure distillation, yielded a crystalline compound, m. p. 71-72°. The infrared spectrum showed -NH bands at 3250 and 3080 cm^{-1} (105) and amide bands at 1675 and 1560 cm^{-1} (106). Elemental analysis showed this compound to have the composition, $C_{12}H_{16}N_2O_2$. From the elemental analysis, showing a loss of four carbon atoms, and the -NH bands in the infrared spectrum, it appeared that the ketone portion of the molecule had been removed and that the compound, $C_{12}H_{16}N_2O_2$, could be represented by either of the two structures shown below.

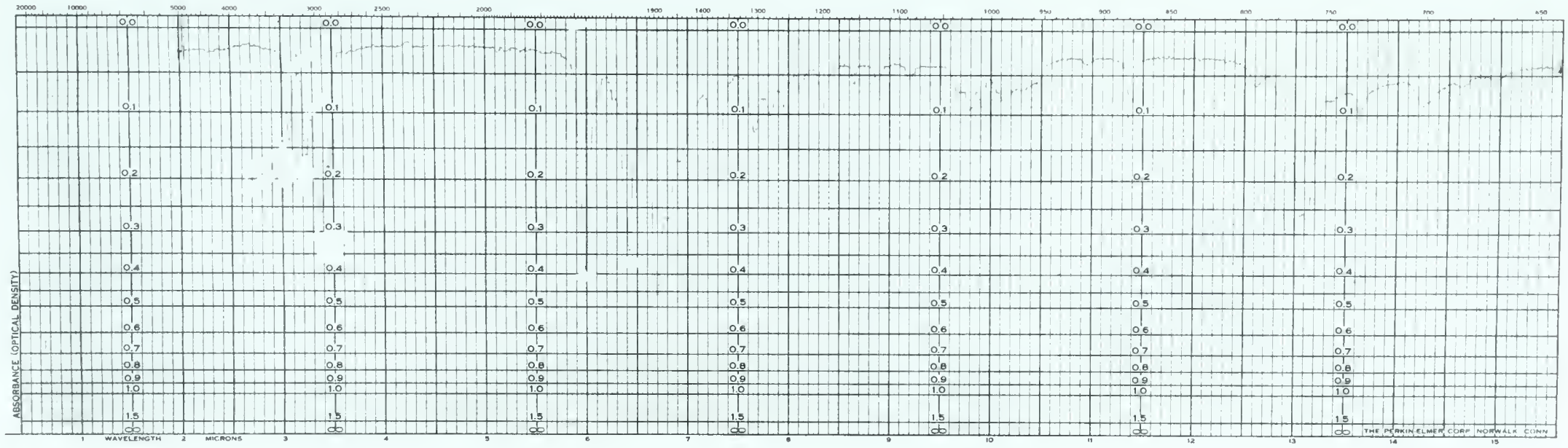
It was realized that positive identification of this compound would depend upon some method of selectively cleaving the N=N bond of the molecule and identification of the resulting fragments. Reductive cleavage of the nitrogen-nitrogen bond in carboxylic acid hydrazides and in 1,2,-diacylated hydrazines has been accomplished by refluxing these compounds in ethanol in the presence of a large excess of Raney nickel (107, 108). In a study of the scope of this reaction Hinman (109) found that several previously reported resistant

compounds could be cleaved by extending the reaction time from the usual 3 hours to one of 15 - 20 hours. It was thought that this method might be useful in identifying the compound, $C_{12}H_{16}N_2O_2$. Thus we refluxed our unknown compound with excess Raney nickel in ethanol for 20 hours. Removal of the Raney nickel and evaporation of the solvent afforded 2,6-dimethylacetanilide in 15% yield. No acetamide was isolated. An authentic sample of 2,6-dimethylacetanilide (110) gave an identical infrared spectrum and a mixture melting point showed no depression. This suggested that our acetylated hydrazine, $C_{12}H_{16}N_2O_2$, was N,N'-diacetyl-2,6-dimethylphenylhydrazine rather than the unsymmetrically diacylated isomer. Since this reduction technique might prove useful to us in identifying other molecules of this type, and in view of the success of these reagents in reducing nitro compounds (111), we decided to use Raney nickel and hydrazine in an attempt to improve Hinman's procedure (109) for the cleavage of N—N bonds. Details of this modification are described in section E of this discussion. When this modified reduction procedure (112) was used with the above diacetyl-2,6-dimethylphenylhydrazine, we obtained a 68% yield of 2,6-dimethylacetanilide plus a 45% yield of acetamide. No 2,6-dimethyl aniline and diacetamide were isolated. This proves, then, that our diacetyl-2,6-dimethylphenylhydrazine was indeed N,N'-diacetyl-2,6-dimethylphenylhydrazine. An authentic sample of N,N'-diacetyl 2,6-dimethylphenylhydrazine was prepared (112) and was identical in all respects to the compound we had isolated. The infrared spectrum of this

compound is shown in Figure 4. Thus, the unstable methyl ethyl ketone 2,6-dimethylphenylhydrazone had not survived the vigorous acetylation conditions, but had undergone cleavage either during the acetylation or during the reduced pressure distillation which followed.

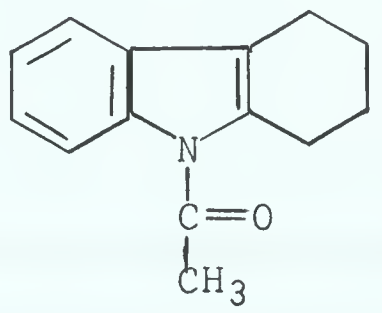
Suvorov (62) had successfully prepared the diacetyl derivative of methyl ethyl ketone phenylhydrazone by acetylation with acetic anhydride at room temperature using an equimolar amount of p-toluenesulfonic acid instead of the catalytic amount employed with refluxing acetic anhydride. Purification was by reduced pressure distillation as before. It was decided in view of the instability of 2,6-dimethylphenylhydrazones that these milder acetylation conditions might be more suitable for our purposes. Also, we decided to use cyclohexanone as the ketone since its phenylhydrazone might be a solid and thus more easily handled (e.g. cyclohexanone phenylhydrazone is a crystalline solid while methyl ethyl ketone phenylhydrazone is an oil). Cyclohexanone 2,6-dimethylphenylhydrazone was prepared and indeed was a solid (m. p. 38 - 40°), but was very unstable in air and therefore was always used immediately. As a preliminary experiment, cyclohexanone phenylhydrazone itself was acetylated using the milder, room temperature conditions. To avoid reduced pressure distillation, since this might result in cleavage, the reaction mixture was stirred for two hours with aqueous sodium acetate to hydrolyze the excess acetic anhydride, and the acetic acid formed was neutralized with saturated aqueous sodium bicarbonate. The reaction mixture was extracted and

Figure 4



I. R. Spectrum of N,N'-Diacetyl-2,6-dimethylphenylhydrazine in Nujol.

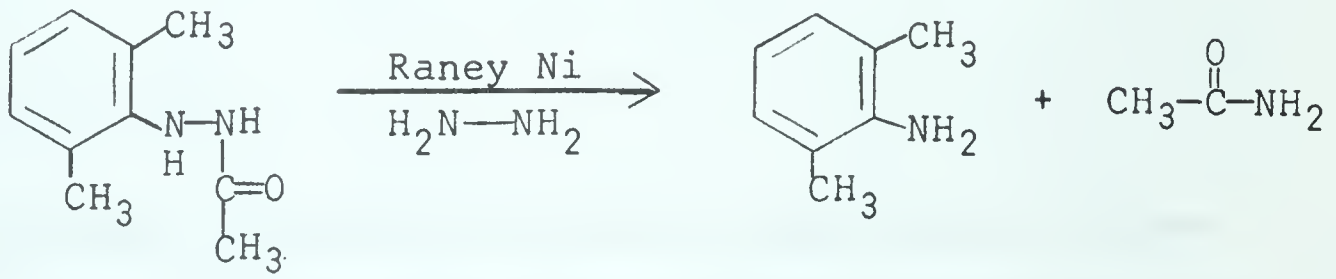
chromatographed on neutral alumina. A white crystalline compound, m. p. 75 - 77°, was isolated. Elemental analysis showed the compound to have the composition, $C_{14}H_{15}NO$. The formula is satisfied by 9-acetyl-1,2,3,4-tetrahydro-



carbazole. Comparison of this compound with an authentic sample of 9-acetyl-1,2,3,4-tetrahydrocarbazole (113) showed it to be identical in all respects. These conditions then showed that (a) at least some acylation occurs, but (b) cyclization also occurs, and (c) perhaps diacylation occurs. Cyclohexanone-2,6-dimethylphenylhydrazone should not cyclize as readily, if at all, under these acetylation conditions because of the presence of the blocking methyl groups. Therefore, cyclohexanone 2,6-dimethylphenylhydrazone was prepared and subjected to the same acetylation conditions as stated above. Chromatography on neutral alumina yielded a single crystalline compound, m. p. 90 - 92°. The infrared spectrum showed bands at 3360 (-NH), 3230 (bonded -NH) and 1650 cm^{-1} (-$\overset{O}{\overset{\|}{C}}$-N) . Elemental analysis showed the compound to have the composition, $C_{10}H_{14}N_2O$. Again it appeared that the ketone portion of the molecule had been cleaved, since the original molecule had the empirical formula, $C_{14}H_{20}N_2$. The compound, $C_{10}H_{14}N_2O$,

could correspond to either of the structures shown below:

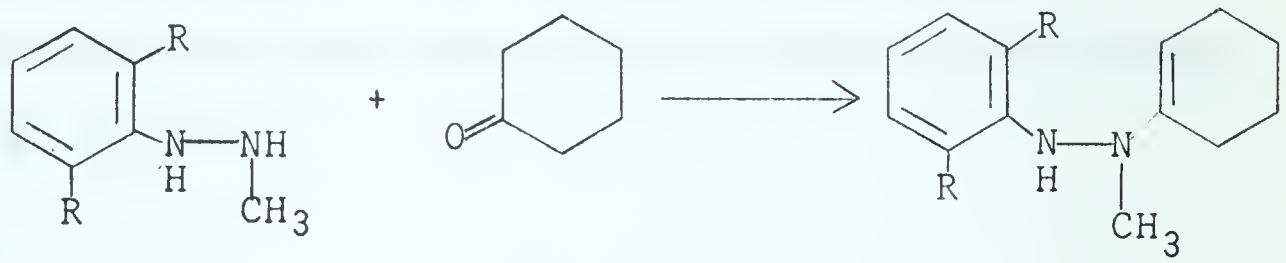
The modified reduction procedure using Raney nickel and hydrazine was again employed to identify the unknown compound. Reduction of the monoacetylated-2,6-dimethylphenylhydrazine yielded acetamide and 2,6-dimethylaniline as the only products. Thus, the correct structure for the monoacetylated-2,6-dimethylphenylhydrazine is N'-acetyl-2,6-dimethylphenylhydrazine.



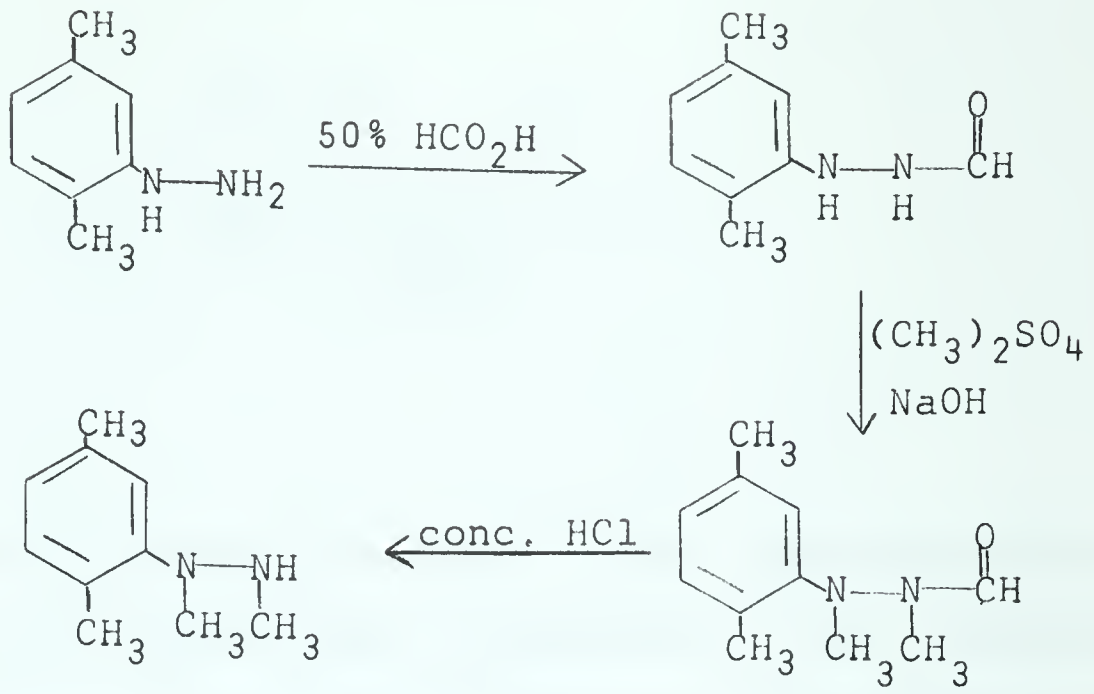
Thus it appeared that even room temperature acetylation conditions are too vigorous for the sensitive 2,6-dimethylphenylhydrazones.

D. Experiments with 2,6-Dichlorophenylhydrazones

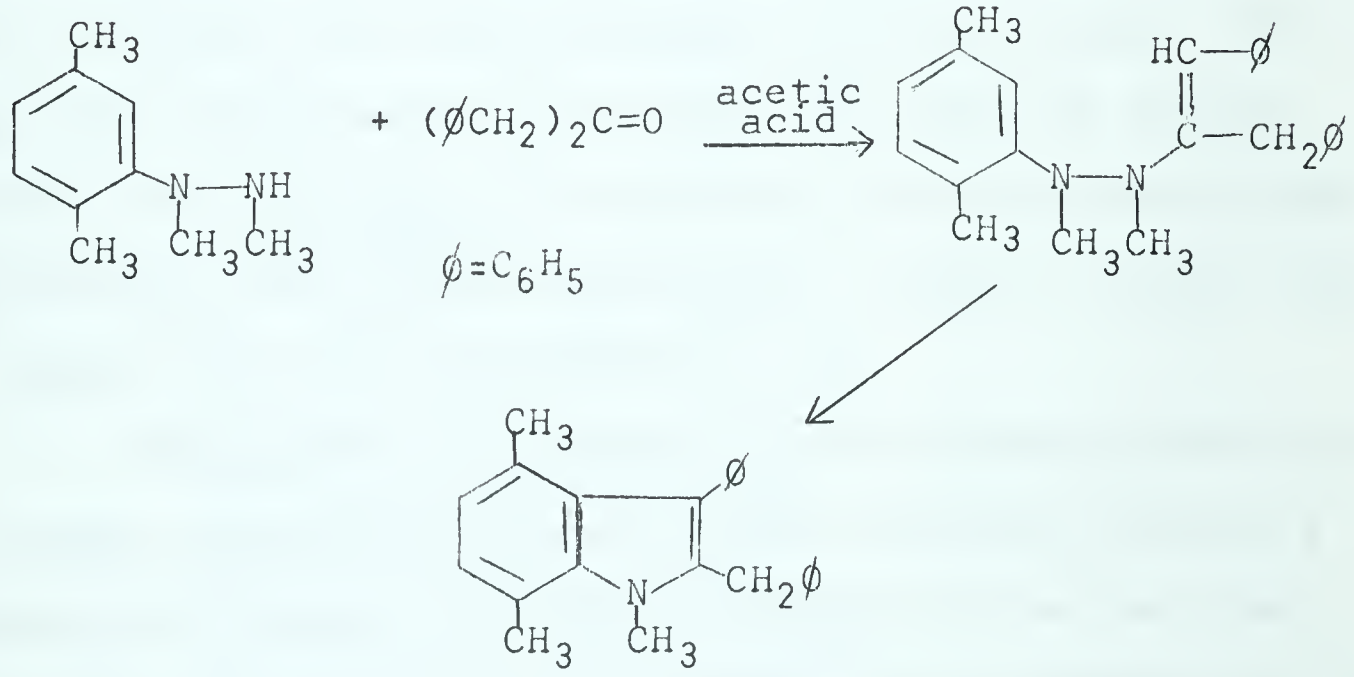
Since all our efforts to obtain the enehydrazine form of 2,6-disubstituted phenylhydrazones by acetylation of these molecules had resulted in only cleavage products, it was thought that alkyl substituents on the nitrogens might better accomplish our aim. Preparation of a β-alkyl-2,6-disubstituted phenylhydrazine, followed by condensation with a ketone under the conditions of Stork's enamine synthesis (114) would give the desired type of compound.



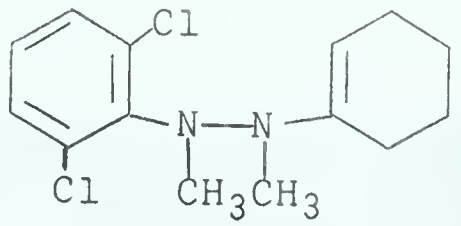
The enamine-type enehydrazine would be particularly advantageous since it is one step further toward products in the proposed mechanism. An α,β-dialkyl-2,6-disubstituted phenylhydrazine could be used equally well. A search of the literature showed that Neber and co-workers (115) had prepared α,β-dimethyl-α-(2,5-xylyl)-hydrazine according to the following sequence:



They also prepared the dibenzylketone derivative of this hydrazine and cyclized this product to the corresponding indole as follows:



We thought it might be possible to use a similar sequence to prepare the following enehydrazine. This enehydrazine

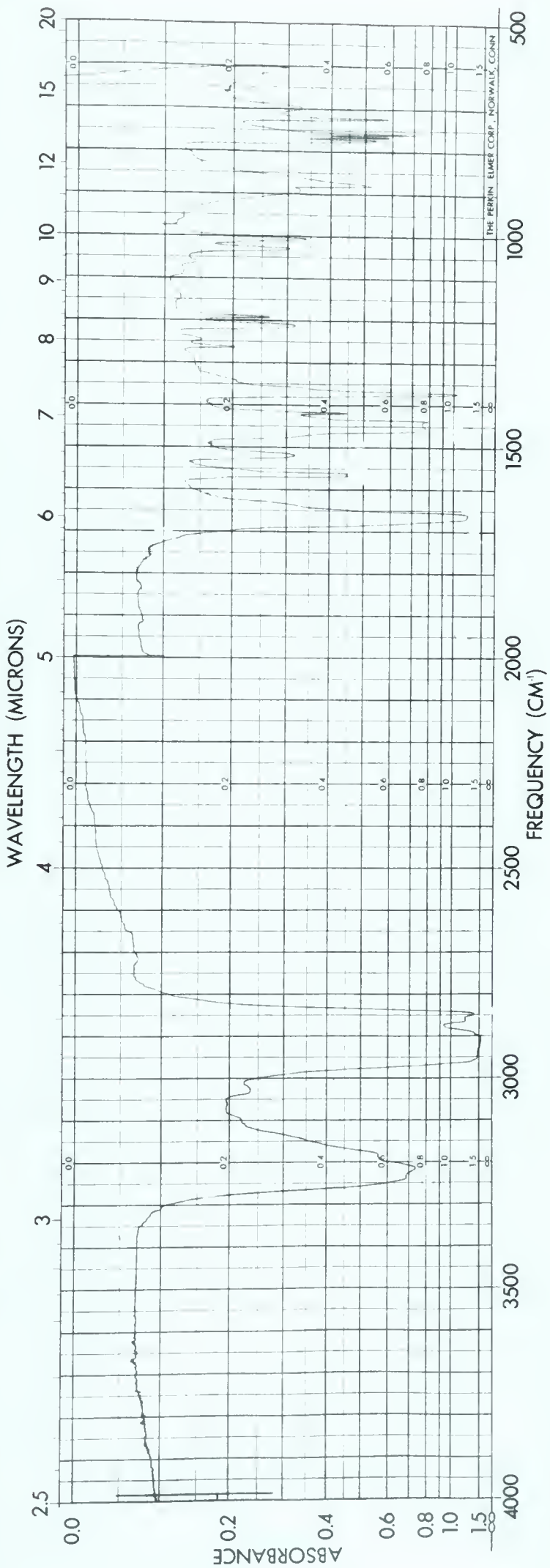


might then be rearranged in order to gain some information concerning the dienone-imine intermediate. The 2,6-dichlorophenylhydrazine was chosen because it is far more stable than 2,6-dimethylphenylhydrazine and cyclohexanone was chosen because it is a ketone which is readily enolizable. Furthermore, the product would most likely be a solid.

Thus, 2,6-dichlorophenylhydrazine was formylated with 50% formic acid to give N'-formyl-2,6-dichlorophenylhydrazine. However, we found that the use of formamide in acetic acid (116) gave better yields of this product. The formyl derivative melted at 160-161° and gave the correct analysis for $C_7H_6N_2Cl_2O$. The infrared spectrum showed bands at 3215(-NH), 1665(-C(=O)-N-) and 1565 cm^{-1} (amide II band) (106). This spectrum is shown in Figure 5.

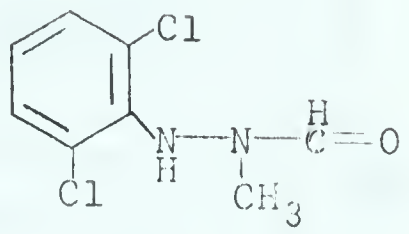
Methylation of N'-formyl-2,6-dichlorophenylhydrazine with excess dimethylsulfate and sodium hydroxide yielded a monomethyl-N'-formyl-2,6-dichlorophenylhydrazine, as shown by the fact that the infrared spectrum still possessed an -NH band. This compound melted at 73-75° and gave analytical values for the formula, $C_8H_8N_2Cl_2O$. Because of the presence of the bulky Cl substituents in the 2- and 6-positions, one

Figure 5



I. P. Spectrum of N'-Formyl-2,6-dichlorophenylhydrazine in Nujol.

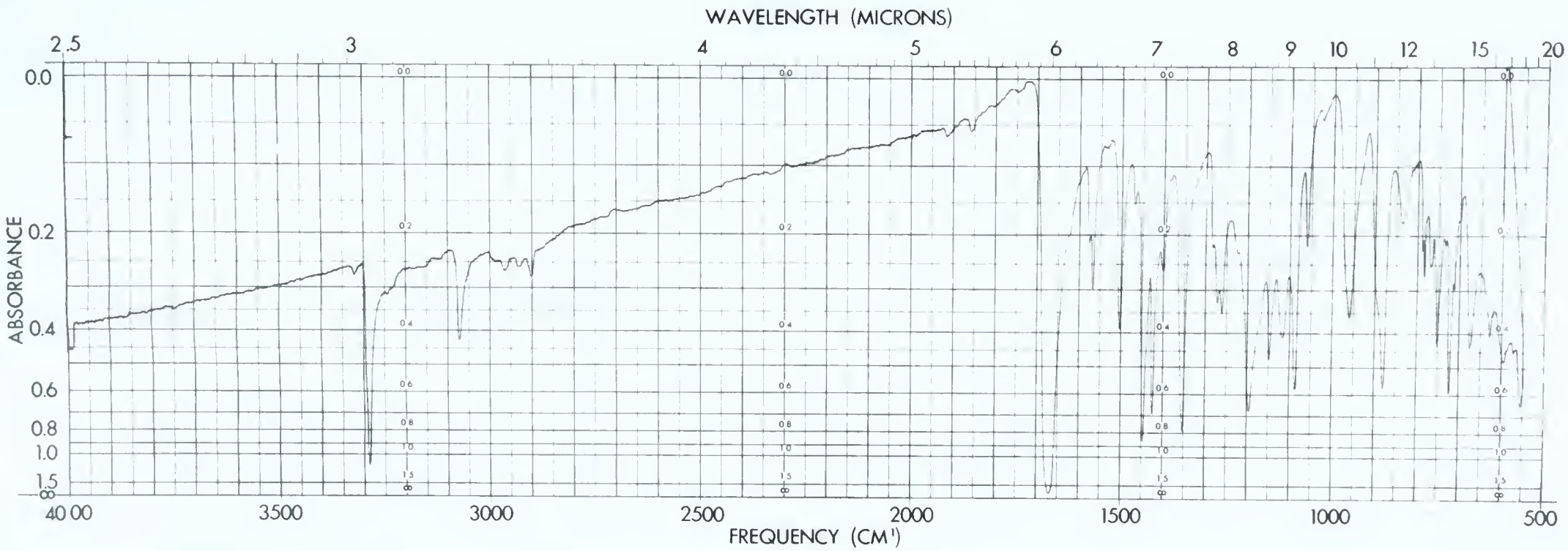
would suppose that this product is N'-methyl-N'-formyl-2,6-dichlorophenylhydrazine, as shown below.



That this is actually the case was shown by Raney nickel and hydrazine reduction of the compound and isolation of 2,6-dichloroaniline as a product (N-methylformamide was not isolated). There was certainly a methyl group attached to nitrogen present in the original dichlorophenylhydrazine, however, as evidenced by the presence of a peak at 7.1 τ in the n.m.r. spectrum. The infrared and n.m.r. spectra of this N'-methyl-N'-formyl-2,6-dichlorophenylhydrazine are shown in Figures 6 and 7, respectively.

The hydrolysis of the formyl methyl hydrazine was carried out with concentrated hydrochloric acid in ethanol. When the reaction mixture was poured into ice water and basified, an oil was obtained. This oil was extracted with ether, the ether solution dried, and the hydrochloride precipitated by bubbling in anhydrous hydrogen chloride. The yield of the hydrochloride was 67%, m. p. 181-182°. Analysis showed the empirical formula to be $C_7H_9N_2Cl_3$, as expected. The infrared spectrum of the N'-methyl-2,6-dichlorophenylhydrazine hydrochloride showed the following peaks:

Figure 6



I. R. Spectrum of N-Formyl-N'-methyl-2,6-dichlorophenylhydrazine in Halocarbon Oil.

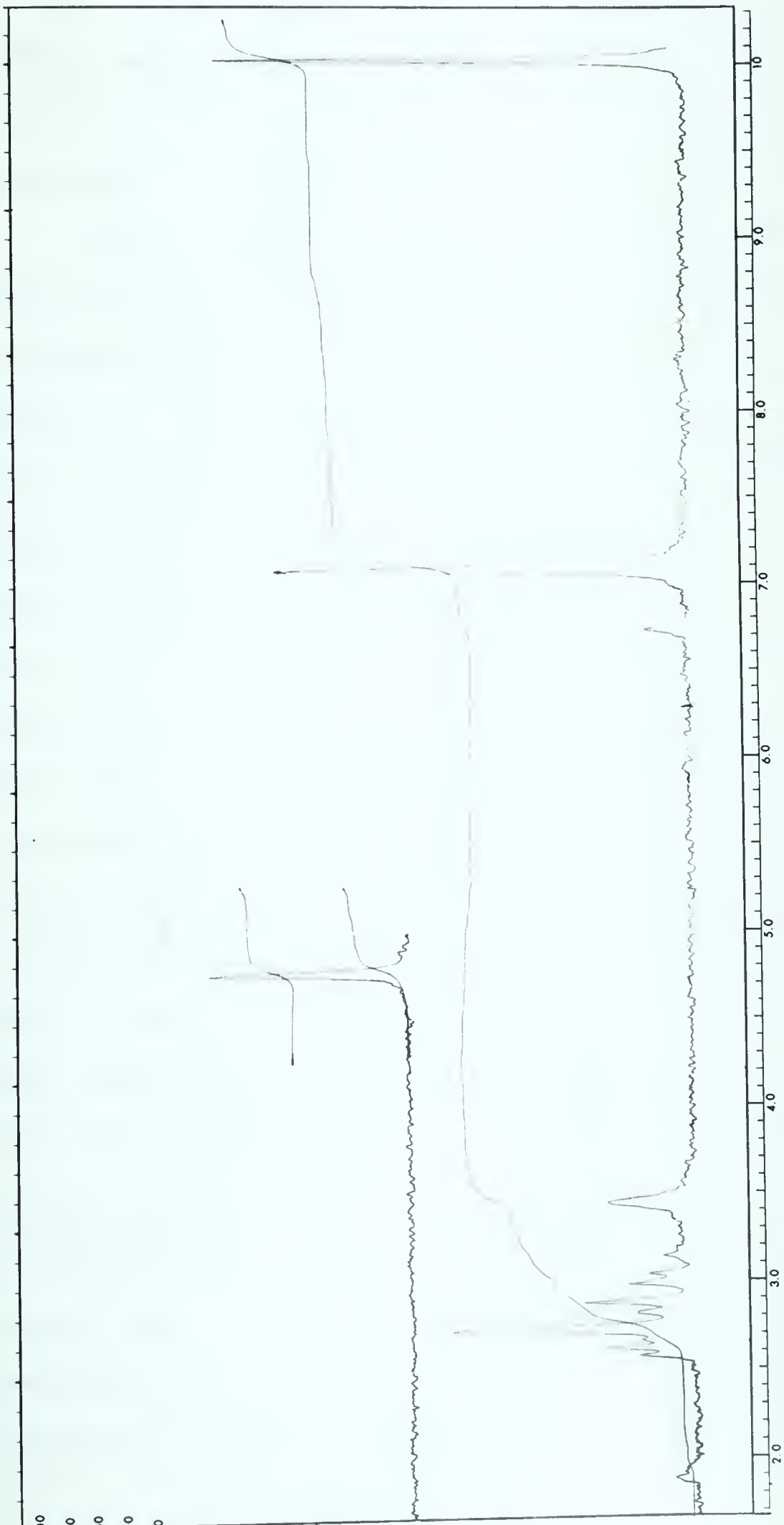


Figure 7. N. M. R. Spectrum of N'-Formyl-N'-methyl-2,6-dichlorophenylhydrazine in $CDCl_3$.

3220(-NH), a broad peak centered at about 2930(-CH_3), 2690 cm^{-1}(-$NH_2^{\oplus}$) (117), and a peak at 1560 cm^{-1} (aromatic C=C). The n.m.r. spectrum in D_2O showed peaks at 7.0 τ(CH_3), 5.3 τ(DOH), and an AB_2 pattern at 2.3 - 2.9 τ. The infrared and n.m.r. spectra of N'-methyl-2,6-dichlorophenylhydrazine hydrochloride are shown in Figures 8 and 9, respectively.

When N'-methyl-2,6-dichlorophenylhydrazine was condensed with cyclohexanone in refluxing benzene, using a Dean-Stark trap to remove the water formed, a white compound precipitated. This compound was filtered from the benzene solution and was found to melt at 180-189°. Surprisingly, it was found that this compound was water-soluble and an aqueous solution of the substance gave a precipitate when silver nitrate solution was added. The n.m.r. spectrum of the substance in D_2O showed, in addition to the DOH peak, only a methyl peak at 7.25 τ. When the 180-189° melting material was recrystallized several times from ethanol, the melting point was raised to 221 - 224°. From the foregoing evidence, it was suspected that this substance was methylamine hydrochloride. Comparison of the n.m.r. spectrum with that of authentic methylamine hydrochloride and a mixture melting point determination showed that the substance obtained was indeed methylamine hydrochloride. The benzene solution remaining after filtration of the methylamine hydrochloride gave a dark yellow oil upon evaporation of the benzene. This oil, which darkened in air, could not be induced to crystallize. Thus, it seemed that some cyclization of the enehydrazine had

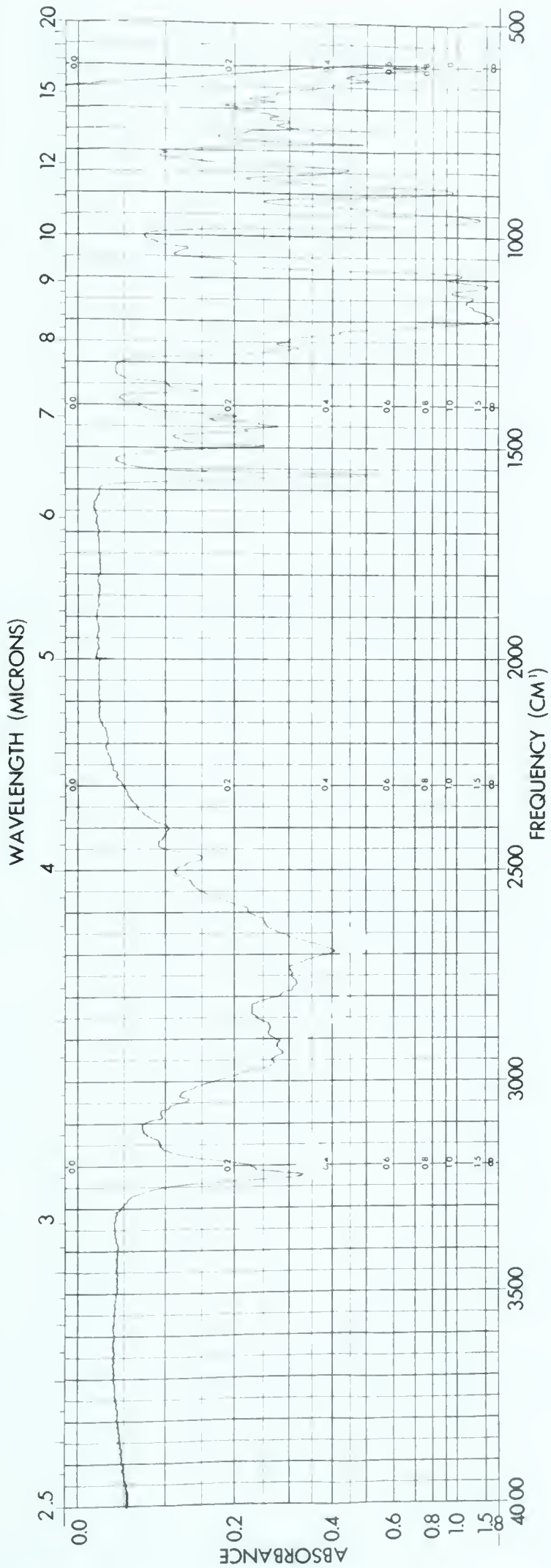
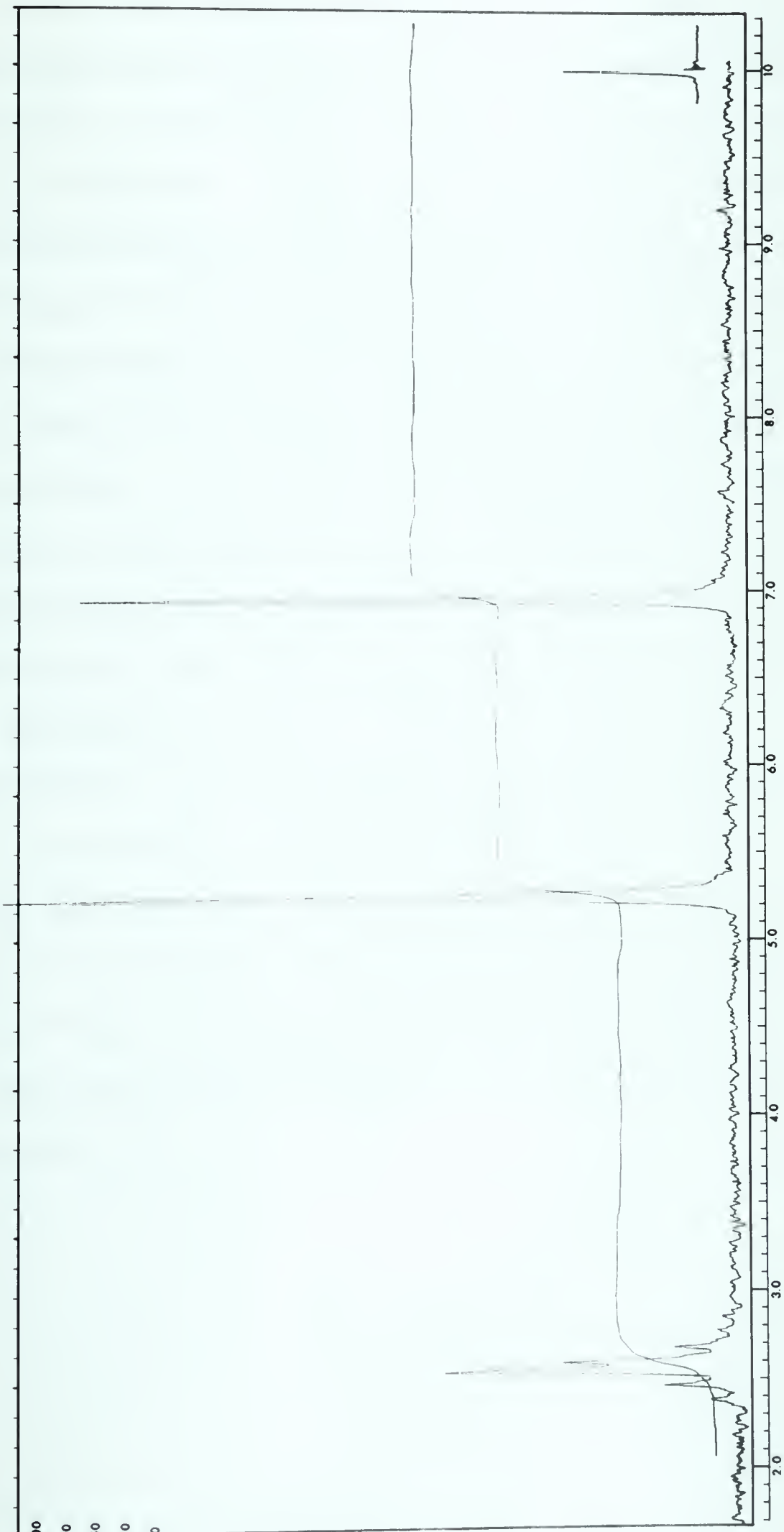


Figure 8

I. R. Spectrum of N'-Methyl-2,6-dichlorophenylhydrazine Hydrochloride in Halocarbon Oil.

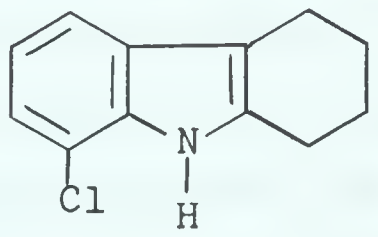
Figure 9



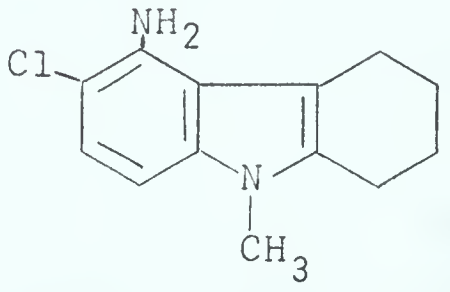
N. M. P. Spectrum of N'-Methyl-2,6-dichlorophenylhydrazine Hydrochloride in D_2O.

occurred in refluxing benzene, producing methylamine hydrochloride as one product.

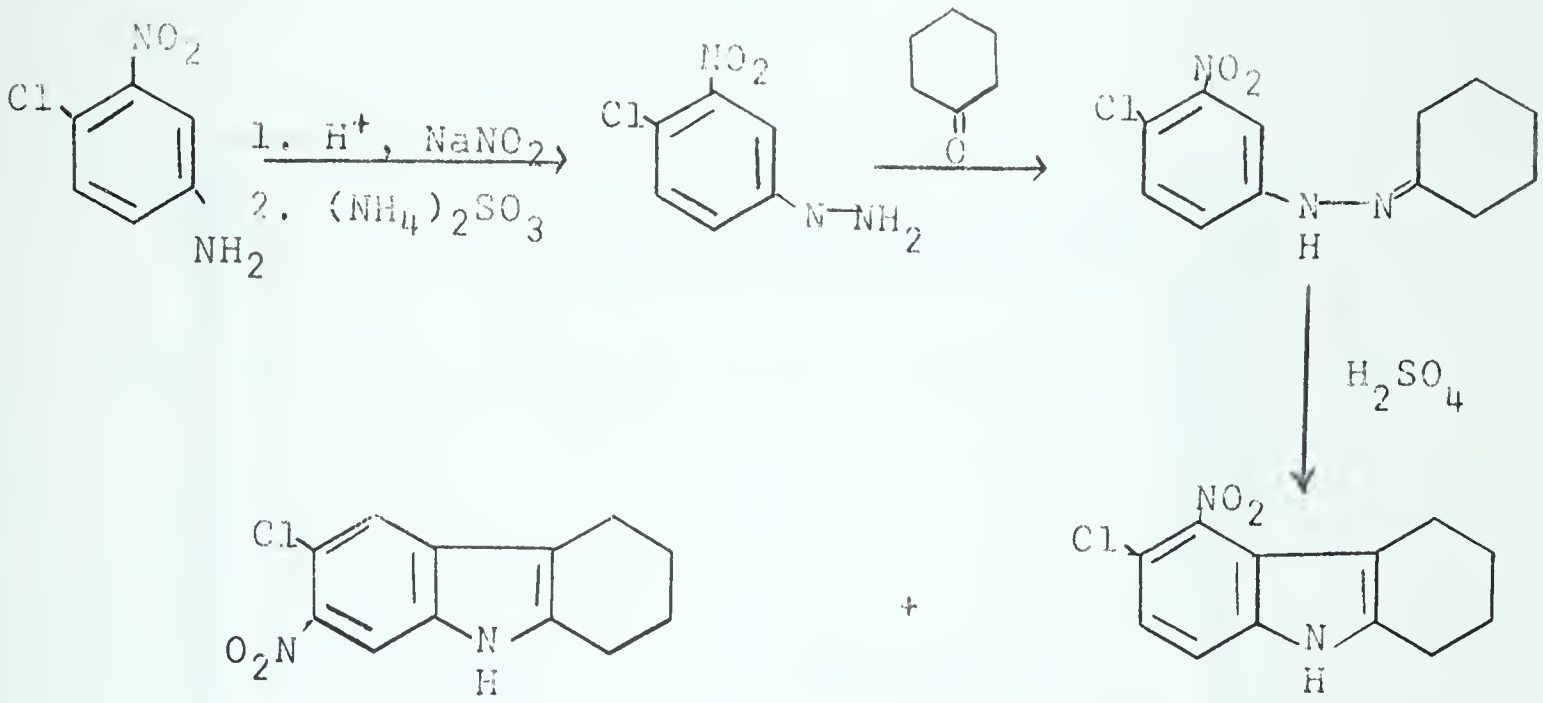
In an attempt to isolate the enehydrazine presumably formed from cyclohexanone and N'-methyl-2,6-dichlorophenylhydrazine, we decided to condense the two substances under milder conditions. Thus, cyclohexanone and N'-methyl-2,6-dichlorophenylhydrazine were combined in benzene and the resulting solution was evaporated on a rotary evaporator while the temperature was kept at 20°. Upon evaporation of about half of the benzene, methylamine hydrochloride again precipitated. Recrystallization from ethanol yielded 0.30g (14.8%) of methylamine hydrochloride melting at 222-225°. The remaining benzene was removed from the filtrate and the resulting oil was chromatographed on neutral alumina. Elution with Skellysolve B gave 0.86g. of a substance melting at 55-56°. The substance was quite unstable and thus no analytical data could be obtained. The infrared spectrum, however, showed bonded -NH(3100 cm^{-1}) and the n.m.r. spectrum showed methylene peaks at 7.29 τ and 8.20 τ and an -NH peak at 1.38 τ. On the basis of the melting point and spectral data, the 55-56° melting material was thought to be 8-chloro-1,2,3,4-tetrahydrocarbazole.



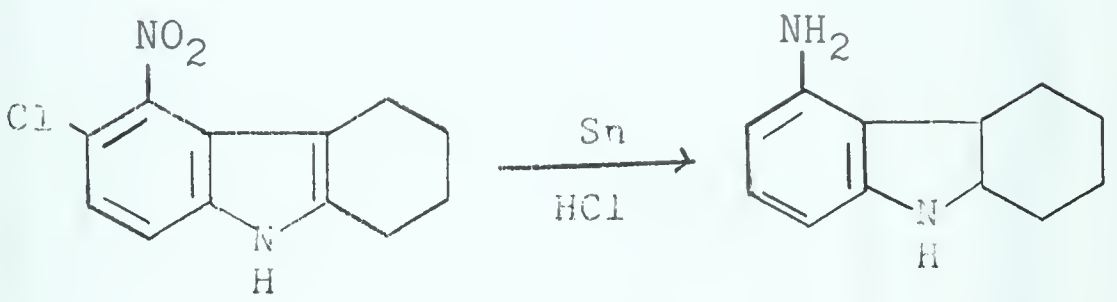
Preparation of an authentic sample of 8-chloro-1,2,3,4-tetrahydrocarbazole (79) and determination of a mixed melting point showed this to be the case. Elution with 1:1 Skellysolve B-benzene gave a slightly discolored substance melting at 87-90°. Recrystallization from ethanol yielded 1.48g of material melting at 90-91°. The n.m.r. spectrum of this 90-91° melting material showed the following peaks: an aromatic AB pattern at 3.0 - 3.8 τ, an NH_2 peak at 5.9 τ, an N-methyl peak at 6.75 τ, and methylene peaks at 7.24, 7.58, and 8.30 τ. This spectrum is shown in Figure 10. Analysis of the compound showed it to have the composition, $C_{13}H_{15}H_2Cl$. On the basis of the n.m.r. spectrum and analytical data, the 90-91° melting material was tentatively assigned the following structure:



To test the correctness of this assignment, it was now necessary to prepare an authentic sample of 5-amino-6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole. A search of the literature showed that Plant and Rosser (118) had prepared 6-chloro-5-nitro-1,2,3,4-tetrahydrocarbazole and 6-chloro-7-nitro-1,2,3,4-tetrahydrocarbazole by carrying out the following sequence:



The two isomers were separated by crystallization but, at the time, were not identified. Later, however, Moggridge and Plant (119) identified one of the isomers as 6-chloro-5-nitro-1,2,3,4-tetrahydrocarbazole by reduction with tin and hydrochloric acid to give the known 5-aminohexahydrocarbazole.



It was assumed that the other isomer was 6-chloro-7-nitro-1,2,3,4-tetrahydrocarbazole. Plant (29) had devised a procedure for methylation of nitrotetrahydrocarbazoles. Thus, we thought we might prepare an authentic sample of 5-amino-6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole by methylation of 6-chloro-

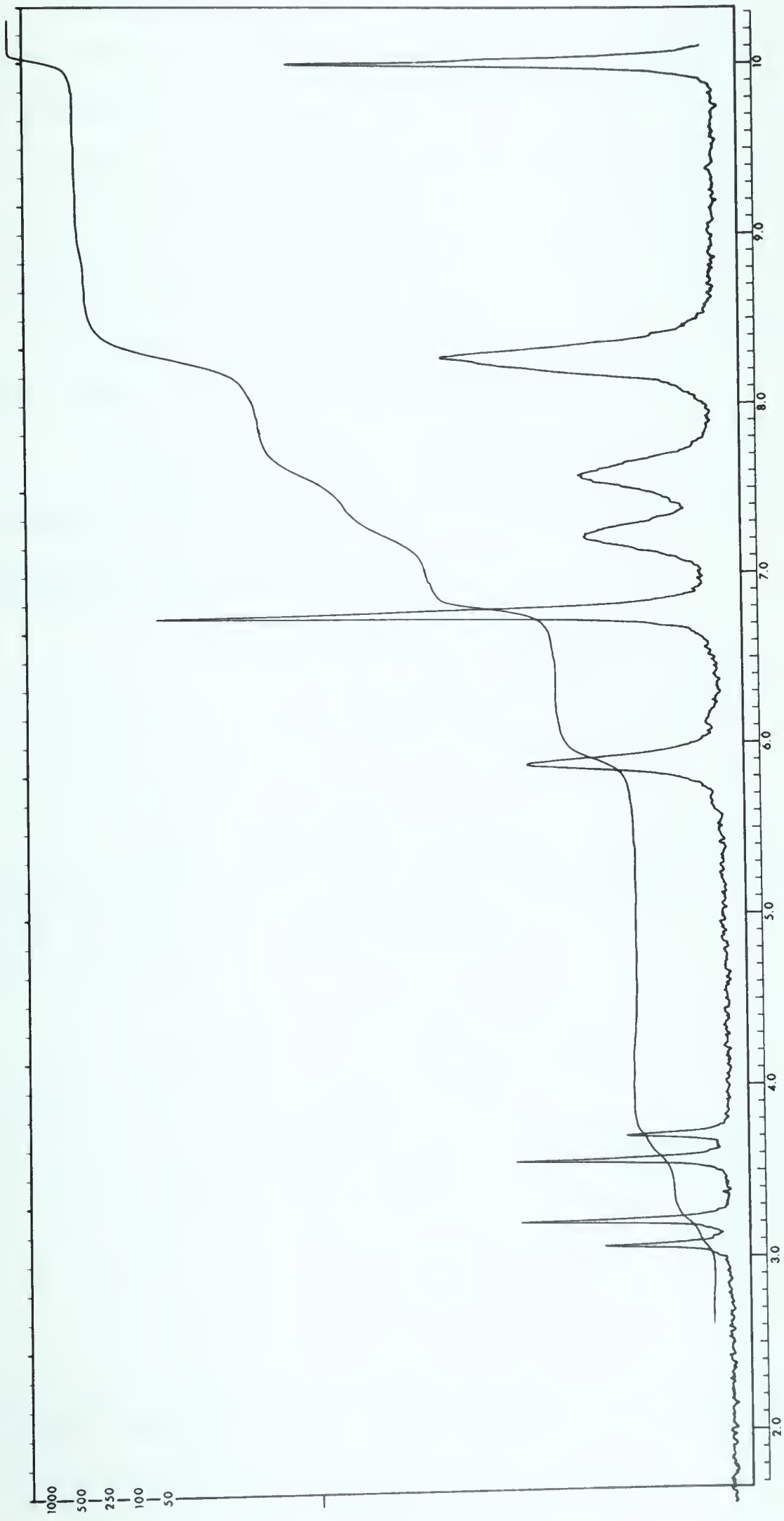


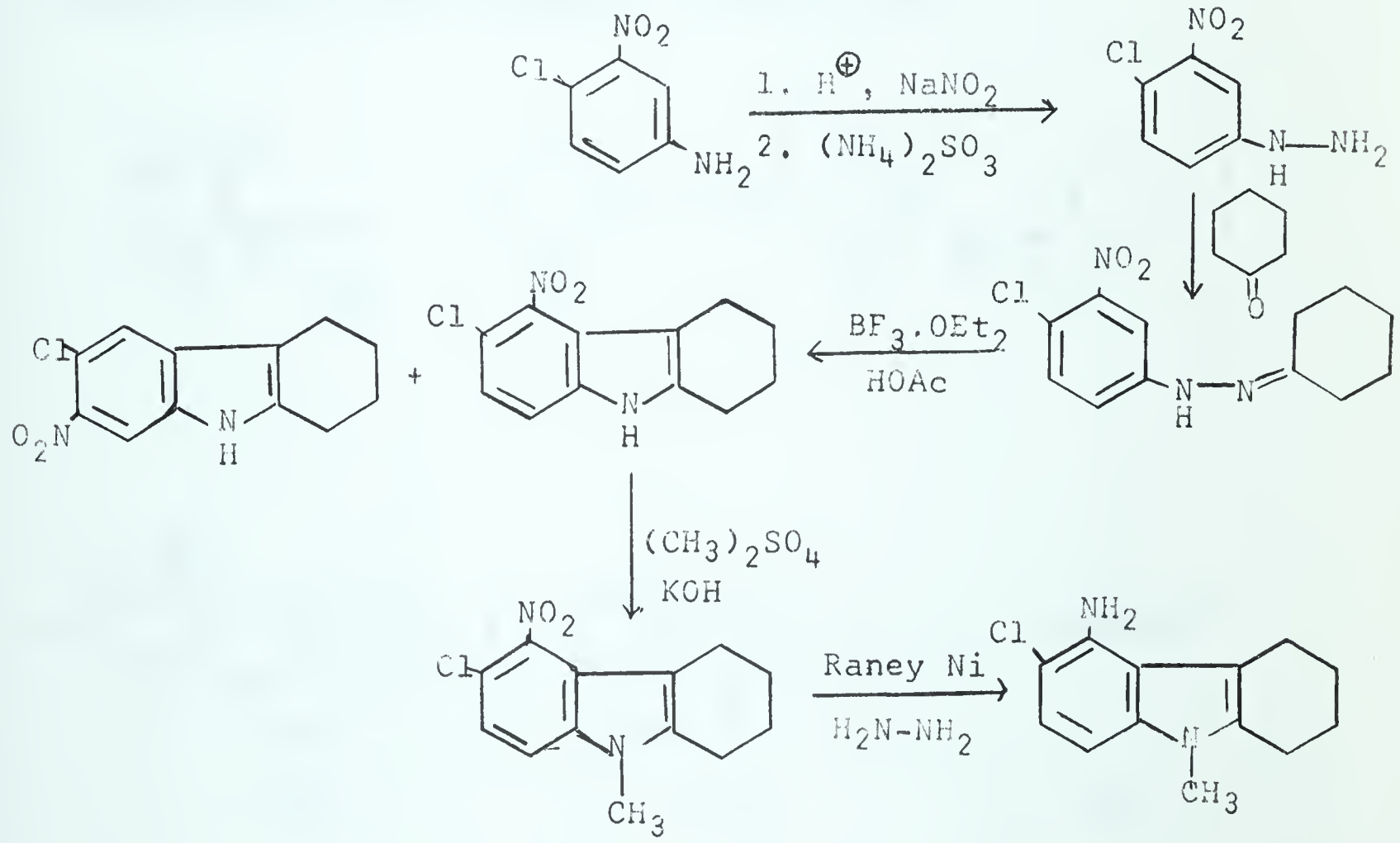
Figure 10

N. M. R. Spectrum (in $CDCl_3$) of $C_{13}H_{15}N_2Cl$ Product from condensation of cyclohexanone and N'-methyl-2,6-dichlorophenylhydrazine.

5-nitro-1,2,3,4-tetrahydrocarbazole followed by reduction of the nitro-group by the procedure of Leggetter and Brown (111).

When we attempted the above sequence, considerable difficulty was experienced in preparing 4-chloro-3-nitrophenylhydrazine. Although Plant and Rosser made no mention of this (118), we found that this phenylhydrazine decomposed to some other substance unless it was purified immediately. We also found that cyclization of cyclohexanone-4-chloro-3-nitrophenylhydrazone worked better if boron fluoride-etherate (14) was used instead of aqueous sulfuric acid.

To summarize, the sequence used by us to synthesize an authentic sample of 5-amino-6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole was as follows:

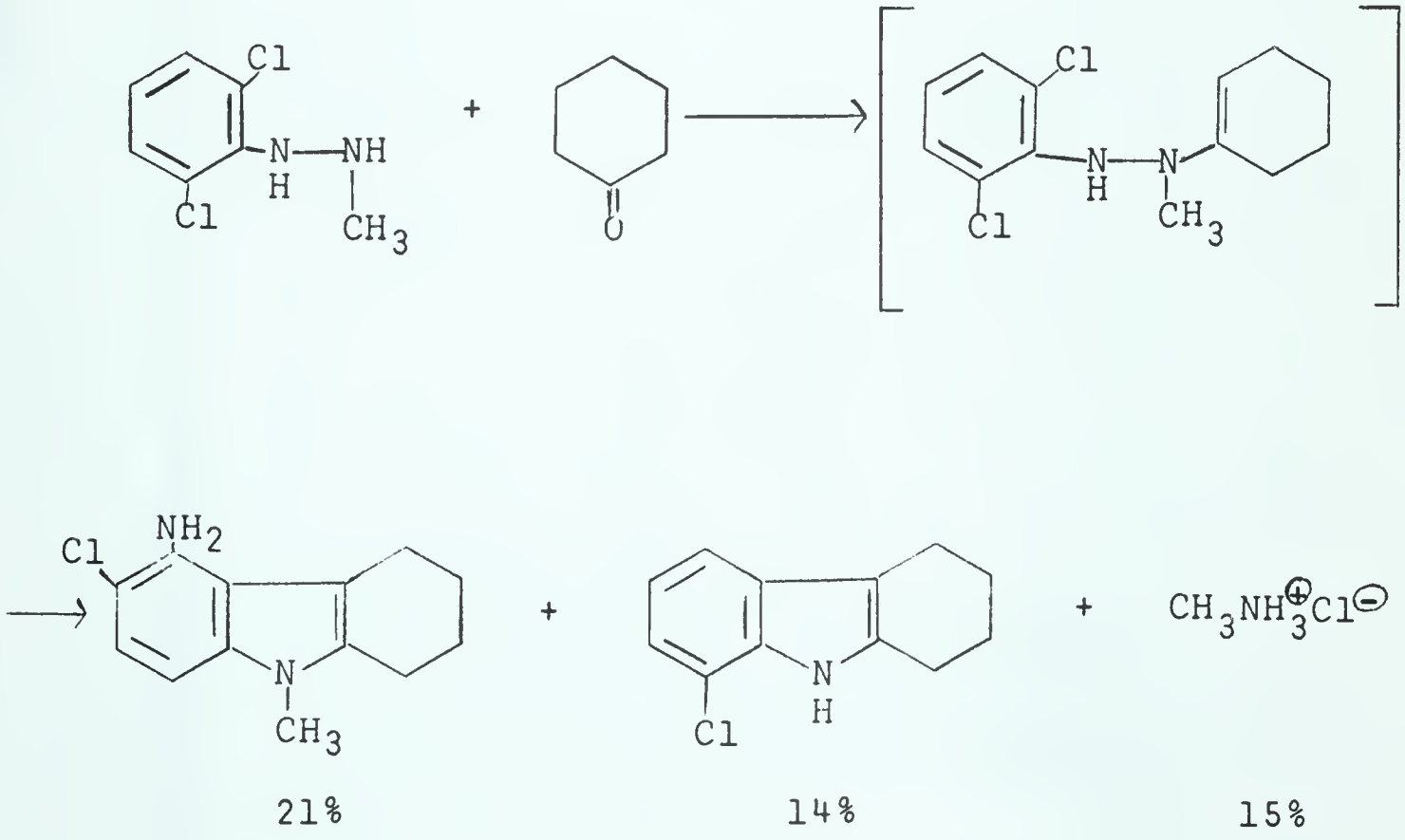


The final product of the above sequence melted at 90-91°,

gave a correct analysis for $C_{13}H_{15}N_2Cl$, showed an identical n.m.r. spectrum to our unknown 90-91° melting material, and showed no depression upon mixture melting point with the unknown. Thus, the $C_{13}H_{15}N_2Cl$ compound obtained by condensation of cyclohexanone and N'-methyl-2,6-dichlorophenylhydrazine was 5-amino-6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole. The n.m.r. spectrum of the authentic material is shown in Figure 11.

1. Interpretation of Results

From the results obtained above, the overall reaction which occurs when cyclohexanone and N'-methyl-2,6-dichlorophenylhydrazine are condensed is as follows:



In our opinion, the isolation of 5-amino-6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole is a significant piece of evidence in

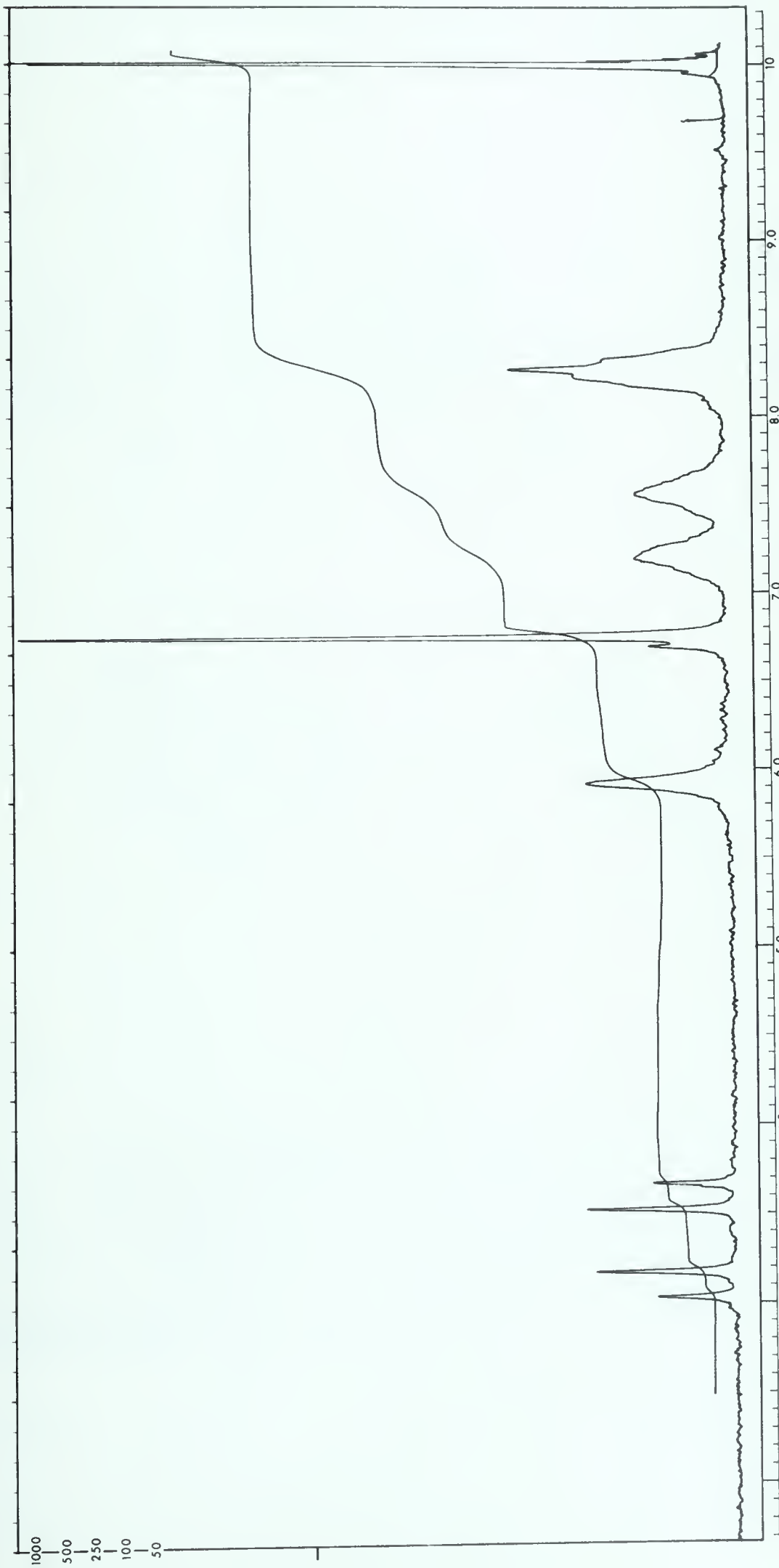
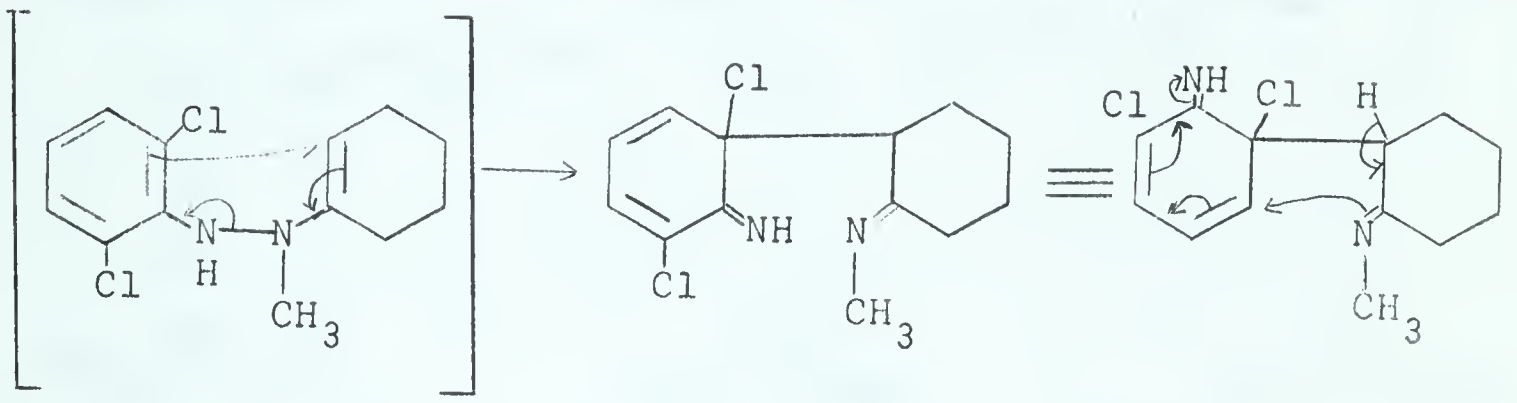
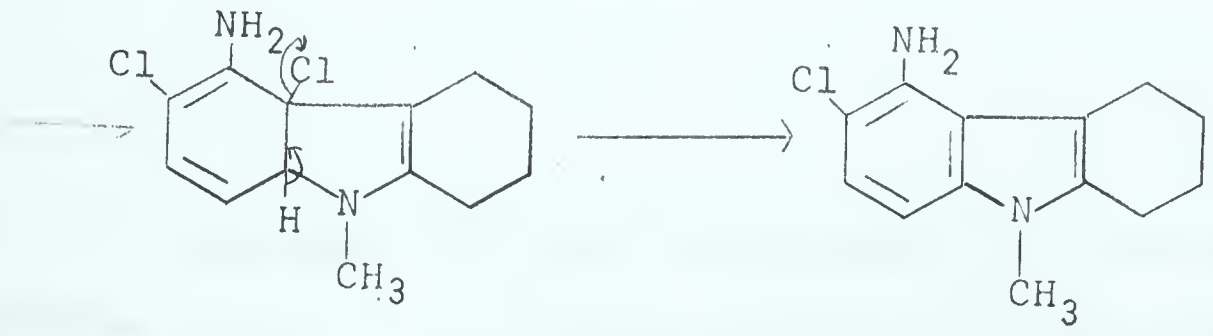


Figure 11

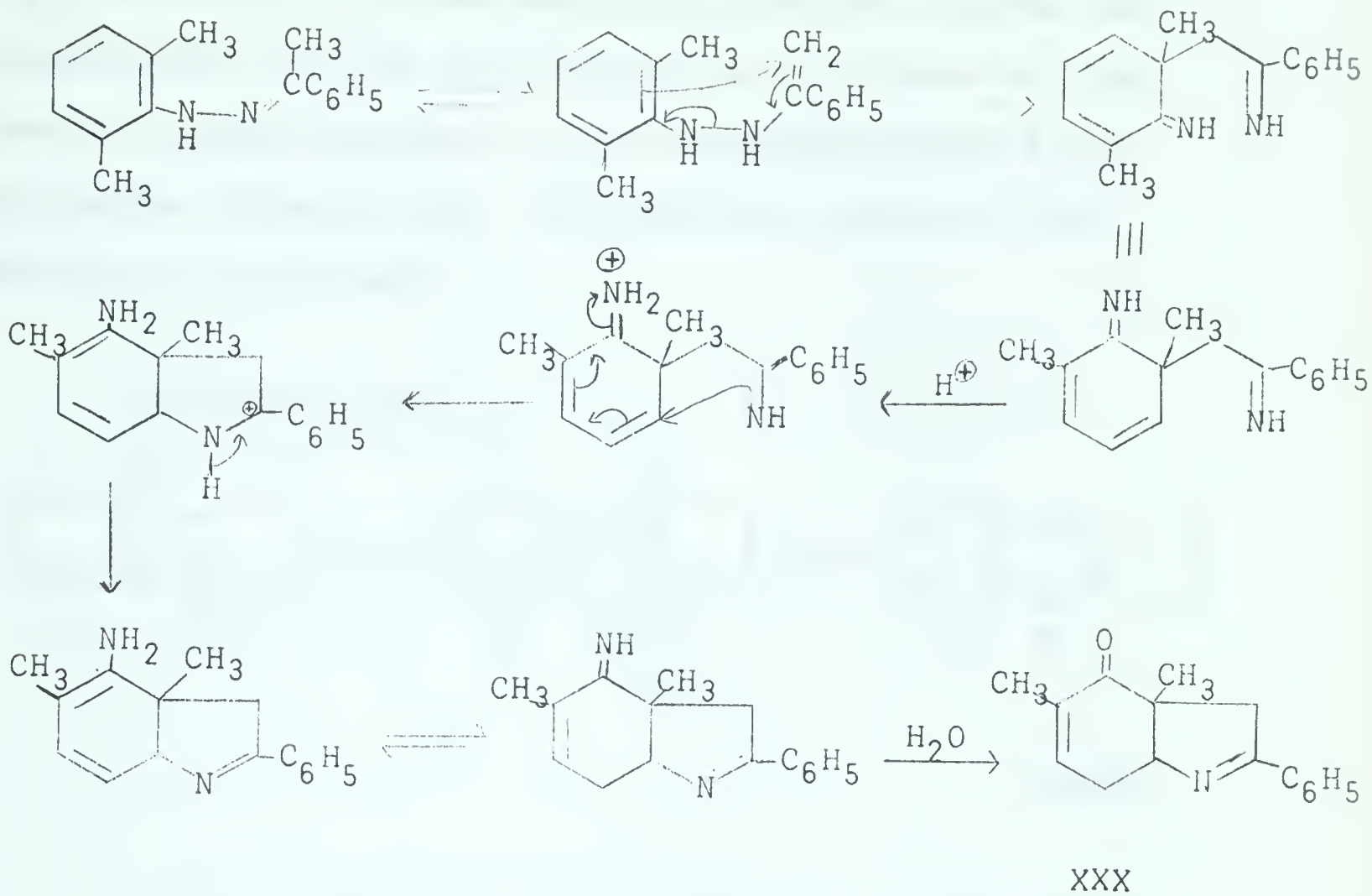
N. M. R. Spectrum (in $CDCl_3$) of Authentic 5-Amino-6-Chloro-9-methyl-1,2,3,4-tetrahydrocarbazole.

favor of the dienone-imine intermediate proposed by Carlin (79 - 86). With the aid of such an intermediate the mechanism for the formation of this substance may be written as shown below.





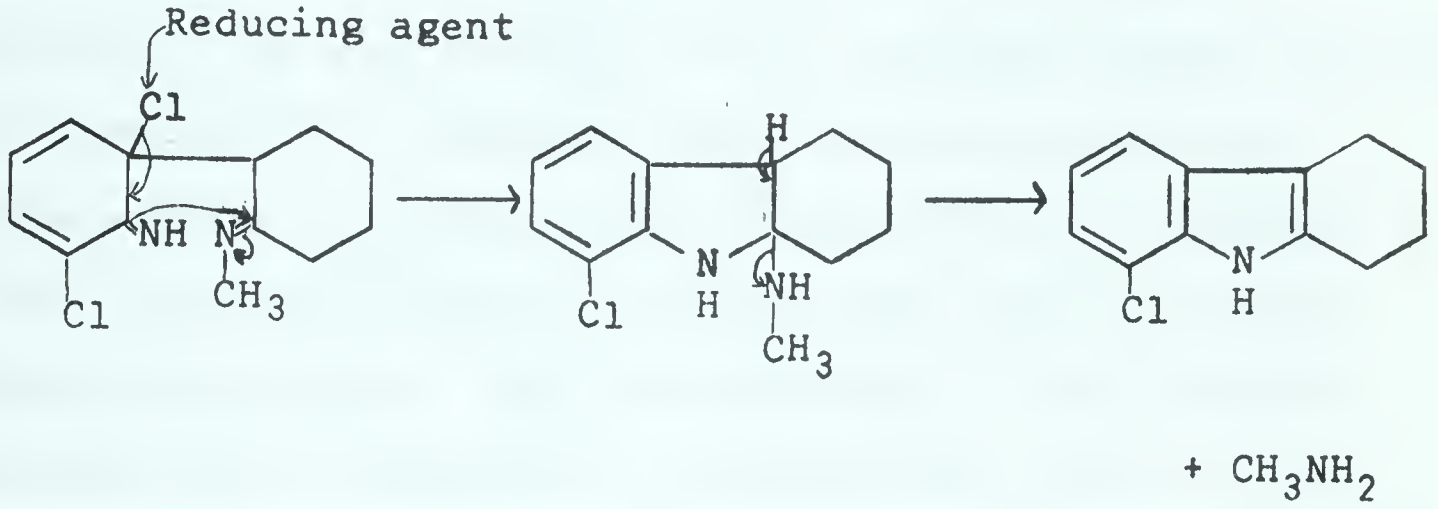
This is somewhat analogous to Carlin's explanation (83, 84) for the formation of 2-phenyl-3a,5-dimethyl-3a,4,7,7a-tetrahydro[3H] pseudoindolone (XXX) from acetophenone-2,6-dimethylphenylhydrazone as shown below:



XXX

Although the product 8-chloro-1,2,3,4-tetrahydrocarbazole cannot be as readily explained via the dienone-imine intermediate, its formation is not without analogy. Piers and Brown (69) reported the formation of 2-allyl-6-chlorophenol during the thermal rearrangement of allyl-2,6-dichlorophenyl ether and Carlin (79) obtained 7-chloroindoles from the stannous chloride catalyzed cyclization of 2,6-dichlorophenylhydrazones. The formation of the "reduction" product in the Claisen rearrangement was suggested as occurring at the dienone stage due to the presence of an oxidizable substance. Thus, we would suggest that some readily oxidizable substance present in the reaction mixture

(e.g., N'-methyl-2,6-dichlorophenylhydrazine) reduces the dienone-imine and that this reduction is followed by ring closure to give 8-chloro-1,2,3,4-tetrahydrocarbazole and methylamine hydrochloride. The possible course of this reaction is as follows:



$+ CH_3NH_2$

To our knowledge this is the first example of a room temperature, non-catalytic Fischer indole synthesis. Failure to isolate the enehydrazine which is formed from cyclohexanone and N'-methyl-2,6-dichlorophenylhydrazine is perhaps due to the electron-donating effect of the N'-methyl group. This would facilitate cleavage of the N—N bond, causing the enehydrazine to rearrange to the dienone-imine which decomposes to products. The value of these very mild conditions is that it now seems possible to isolate products that under the usual, more stringent conditions end up as tars. This reaction appears to be much cleaner. The surprising ease with which conversion of the enehydrazine to the dienone-imine occurs seems to support Suvorov's suggestion (46) that this step need not be acid-catalyzed.

E. Reductive Cleavage of Nitrogen-Nitrogen Bonds with Raney Nickel and Hydrazine (112)

As mentioned in the previous sections of this discussion, it was necessary during the course to our work on the acetylation of phenylhydrazones to identify several mono- and di-acylated phenylhydrazines in which the specfic position of the acyl group(s) on the nitrogen atom(s) was known with certainty. A promising method for this structural determination was thought tc be a mild reductive cleavage of the nitrogen-nitrogen bond which would leave the amide linkage undisturbed. Reductive cleavage of the nitrogen-nitrogen bond in carboxylic acid hydrazides and in 1,2-di-acylated hydrazines has been accomplished by refluxing these compounds in ethanol in the presence of a large excess of Raney nickel (107, 108). In a study of the scope of this reaction Hinman (109) found that several previously reported resistant compounds could be cleaved by extending the reaction time from the usual 3 hours to one of 15 - 20 hours. However, by either of these methods yields were generally only fair, ranging from 5 to 60%. In addition, several compounds failed to reduce even after prolonged reaction.

Recent work on the facile reduction of nitro compounds to amines by hydrazine in the presence of Raney nickel (111, 120, 121) shows that the reduction proceeds, at least in part, by way of the bimolecular reduction inter-mediates, azoxybenzene and hydrazobenzene. Continued reduction

readily converted these in turn to the corresponding amine. It was therefore thought that the combination of Raney nickel and hydrazine would reductively cleave nitrogen-nitrogen bonds much more readily than would Raney nickel alone. A series of experiments showed that this was indeed the case.

When hydrazine hydrate was added dropwise over a period of 1 hour to refluxing methanol containing equal weights of acylated phenylhydrazine and Raney nickel, as smooth reaction occurred giving good yields of the expected products. Presumably the hydrazine is decomposed by the Raney nickel to give ammonia, nitrogen and hydrogen as is the case with platinum black (122).

$$3N_2H_4 \longrightarrow 2NH_3 + 2N_2 + 3H_2.$$

Results of typical reductions are shown in Table I. The amides which formed were quite unaffected by the reducing medium hence it was possible to deduce the position of the acyl group(s) in mono-or di-acylated phenylhydrazines. By this means it was easily shown that the diacetylation of 2,6-dimethylphenylhydrazine with acetic anhydride did in fact form N,N'-diacetyl-2,6-dimethylphenylhydrazine rather that the unsymmetrically acylated isomer. The symmetrically acylated product had been expected by Michaelis and Schmidt from a similar acetylation of phenylhydrazine (123).

The advantages of this method are that short reaction times are required, the yields are generally good, and the products are easy to isolate. An interesting point

Table I

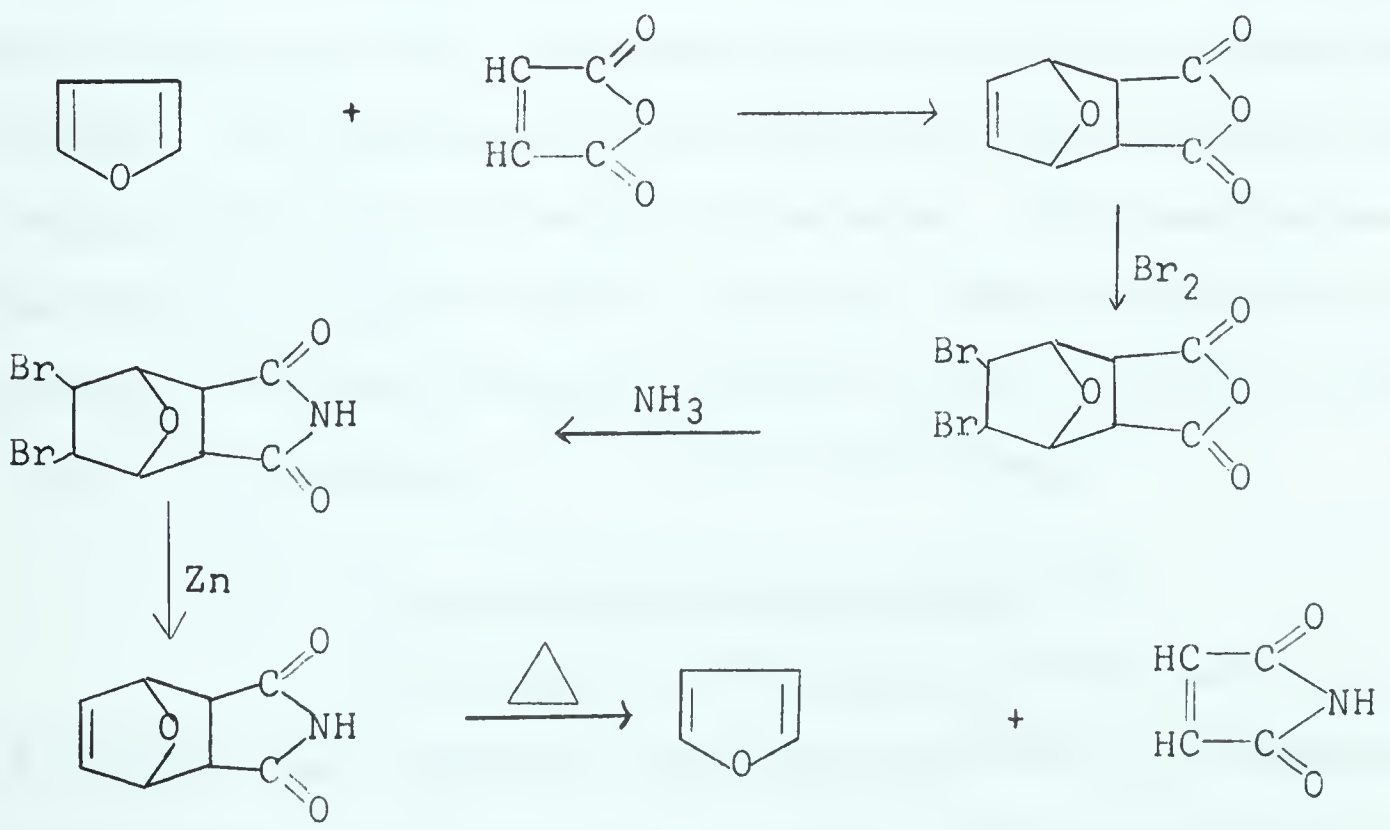
Raney Nickel-Hydrazine Reductions

Compound reduced	Reference to Preparation	Product	Reference to Prepartion of Product	% yield of Product
N,N'-Diacetyl-2,6-dimethylphenylhydrazine	see exptl. section	N-Acetyl-2,6-dimethylaniline plus acetamide	(110) a	68 45
Maleic acid phenylhydrazide	(95)	Maleamic acid anilide	(125, 126)	81
N,N'-Diacetylphenylhydrazine	(123)	Acetanilide plus acetamide	(127) a	73 51
Maleic hydrazide	(128)	Maleamide	(129)	66
N'-Acetyl-2,6-dimethylphenylhydrazine	see exptl. section	2,6-Dimethylaniline plus acetamide	a,b a	60 36
N'-Formyl-N'-methyl-2,6-dichlorophenylhydrazine	see exptl. section	2,6-Dichloroaniline (plus N-methyl formamide)	(130) c	71

a. A commercial sample was used.
b. Identified as 2,6-dimethylacetanilide.
c. Not isolated.

is that the quality of the Raney nickel apparently is unimportant since freshly prepared W-2 Raney nickel (124) gave no better results than those obtained with Raney nickel which had been prepared previously (124) and kept for a period of 6 months under methanol in a refrigerator before use in this reaction. This aged Raney nickel had lost its pyrophoric activity completely.

The synthetic value of this reductive cleavage is shown in the simple <u>two-step</u> preparation of maleamic acid anilide (example 2, Table I) by the reductive cleavage of maleic acid phenylhydrazide, the product of the reaction of phenylhydrazine and maleic anhydride (95). Maleamic acid anilide has been made previously by reaction of aniline with maleimide (125), the latter compound being formed in reasonable yield by a <u>five-step</u> synthesis devised by Berson and co-workers (126) as shown below.



III Experimental

A. Preparation of Phenylhydrazines

(1) ∝-Methyl-∝-phenylhydrazine (131)

A mixture of 200g. (3.1 moles) of zinc dust and 300 ml. of water was stirred vigorously while a solution of 100g. (0.73 mole) of N-nitrosomethylaniline in 200 ml. of glacial acetic acid was added in a slow stream. The temperature was maintained between 10° and 20° by external cooling. When all the acid solution had been added the mixture was stirred for an additional hour at room temperature and then warmed to 80° on the steam bath. The hot solution was filtered from the unreacted zinc, which was washed with three 100 ml. portions of a warm 5% hydrochloric acid solution. The combined filtrate and washings were cooled and treated with sufficient 50% sodium hydroxide solution to dissolve the precipitated zinc hydroxide. The oily layer was separated and the aqueous layer extracted with three 100 ml. portions of ether. The combined oil and extracts were distilled from a steam bath until the ether was removed. The residue was then distilled under reduced pressure. The yield of colorless ∝-methyl-∝-phenylhydrazine boiling at 105 - 108°/12 mm was 44.5g.(51%).Reported b. p., 106 - 109°/13 mm.

(2) 2,6-Dimethylphenylhydrazine (84)

With vigorous stirring 43g (0.36 mole) of 2,6-xylidine was added to a solution of 89 ml. of concentrated hydrochloride acid in 40 ml. of water. The mixture was

chilled to -5°, while stirring was maintained, and a solution of 26.2g. (0.38 mole) of sodium nitrate in 40 ml. of water was added dropwise. The clear orange diazonium solution was maintained at about 0° and stirred while a solution of 180g. (0.80 mole) of stannous chloride dihydrate in 240 ml. of a 1:1 solution of hydrochloric acid in water was added over a 4 hour period. The yellowish slurry was stirred as it was permitted to warm to room temperature and stirring was continued for another 24 hours. The pale yellow tin complex salt was collected by filtration, dried on the funnel and washed with ether. The dry complex salt was stirred into 260 ml. of water and the slurry was stirred vigorously while it was treated with a solution of 90g of sodium hydroxide in 120 ml. of water. The temperature of the mixture was maintained at or below 15°. When the reaction was completed the crude hydrazine was extracted from the mixture with two 140 ml. portions of ether, and then the ether solutions were washed with water and dried over magnesium sulfate. The dried ether solution was diluted with ether to 600 ml., the diluted solution was divided into two equal parts, and each was treated with dry HCl until precipitation of the hydrazine hydrochloride was complete. The filtered hydrochloride was washed with ether and dried. The yield of the hydrazine hydrochloride was 42p. (69%), m.p. 203-205° dec. Reported m. p. , 204° dec.

(3) 2,6-Dichlorophenylhdyrazine (50)

a. 3,5-Dichlorosulfanilamide (130)

To a mixture of 50g. (0.29 mole) of sulfanilamide and 500 ml. of water was added 50 ml. of a 500 ml. portion of

concentrated hydrochloric acid and the mixture was stirred vigorously until a clear solution resulted. The remainder of the 500 ml. of hydrochloric acid was then added. When the temperature of the solution reached 45°, 65g. (59 ml., 0.58 mole) of 30% hydrogen peroxide was added and rapid stirring was initiated. The temperature of the reaction mixture began to rise and the solution deposited a white precipitate which rapidly turned pink. When the temperature of the reaction mixture reached 60°, any further rise in temperature was prevented by external cooling. The reaction was allowed to proceed for 15 minutes at 60° and then the mixture was cooled while stirring was continued. When the temperature had fallen to 25°, the mixture was filtered at once. The yield of crude 3,5-dichlorosulfanilamide was 45g. (65%), m. p. 200 - 203°. Reported m. p., a range of 1 - 2° in the region 200 - 205°.

b. 2,6-Dichloroaniline (130)

The 45g. of crude 3,5-dichlorosulfanilamide was added to 225 ml. of 70% sulfuric acid and the resulting mixture was boiled gently for 2 hours. The dark mixture was then poured into 1 liter of water and the resulting mixture was steam-distilled into a collecting vessel cooled by an ice bath. The white solid product which separated from the distillate was filtered and air dried. The yield of 2,6-dichloroaniline was 24.5g. (77%), m. p. 38 - 40°. Reported m. p. 39 - 40°.

c. 2,6-Dichlorophenylhydrazine (50)

Five hundred ml. of concentrated hydrochloric acid was stirred into a solution of 25g. (0.154 mole) of 2,6-di-

chloroaniline in 100 ml. of glacial acetic acid at room temperature and the resulting solution was cooled to 0°. The mixture was treated with a solution of 11g. (0.16 mole) of sodium nitrite in 40 ml. of water, and the cold solution of the diazonium salt was filtered rapidly and treated dropwise with a cold solution of 100g. (0.45 mole) of stannous chloride dihydrate in 100 ml. of concentrated hydrochloric acid. The insoluble complex salt was collected by filtration, washed with a little saturated aqueous sodium chloride, and the 2,6-dichlorophenylhydrazine was liberated from the salt by treatment of the latter with aqueous sodium hydroxide. The product was extracted with ether, and the ether solution was concentrated until crystallization of the dichlorophenylhydrazine occurred. The crude product weighed 24.3g., m. p. 98- 100°. Recrystallization from ether yielded 21.6g. (76%) of 2,6-dichlorophenylhydrazine, m. p. 99 - 101°. Reported m. p. 100.5 - 101.5°.

4. o-Chlorophenylhydrazine (79)

The above procedure was repeated using 19.6g. (0.154 mole) of o-chloroaniline. The yield of o-chlorophenylhydrazine melting at 44 - 45° was 17.1g. (78%). Reported m.p., 45°.

5. N'-Methyl-2,6-dichlorophenylhydrazine

a. Formylation of 2,6-Dichlorophenylhydrazine (116)

To a solution of 33.6g. (0.19 mole) of 2,6-dichlorophenylhydrazine in 150 ml. of glacial acid was added 7.6 ml. (0.19 mole) of formamide in a dropwise fashion. The resulting solution was stirred at room temperature for one hour,

during which the solution thickened with a white precipitate. The thick slurry was diluted with 150 ml. of water and filtered. The crude N'-formyl-2,6-dichlorophenylhydrazine was crystallized from ethanol, yielding 29.6g. (76%) of product melting at 160 - 161°. Calculated for $C_7H_6N_2Cl_2O$: C, 40.99%; H, 2.95%; N, 13.66%; Cl, 34.58%. Found: C,41.09%; H, 3.10%; N, 13.84%; Cl, 34.72%.

b. Methylation of N'-Formyl-2,6-dichlorophenylhydrazine (115)

To a solution of 41g. (0.20 mole) of N'-formyl-2,6-dichlorophenylhydrazine in 200 ml. of dimethylsulfoxide, 21.4 ml. (0.22 mole) of dimethyl sulfate and a solution of 8.8g. (0.22 mole) of sodium hydroxide in 20 ml. of water were both added dropwise. The resulting solution was stirred for ½ hrs. and diluted with 150 ml. of water. An oil separated which solidified on cooling. The oily solid was filtered and recrystallized from Skellysolve B, yielding 27.6g. (63%) of N-formyl-N'-methyl-2,6-dichlorophenylhydrazine, m. p. 73 - 75°. Calculated for $C_8H_8N_2Cl_2O$: C, 43.86%; H, 3.68%; N, 12.79%; Cl, 32.37%. Found: C, 43.57%; H, 3.64%; N, 12.71%; Cl, 32.54%. The fact that the methyl group was on the N'-nitrogen was shown by Raney nickel-hydrazine reduction of the compound and isolation of the known 2,6-dichloroaniline as a product (N-methylformamide was not isolated) (see Table I). There was certainly a methyl group attached to nitrogen present in the original dichlorophenylhydrazine, however, as evidencedby the presence of a peak at 7.1τ in the n. m. r. spectrum (see Figure 7).

c. Hydrolysis of N'-Formyl-N'-methyl-2,6-dichlorophenylhydrazine (115)

A solution of 43.8g. (0.20 mole) of N'-formyl-N'-methyl-2,6-dichlorophenylhydrazine, 80 ml. of concentrated hydrochloric acid, and 50 ml. of ethanol was refluxed for 6 hours. The solution was allowed to cool to room temperature and poured into ice water. An oil separated, which was extracted with ether and the ether solution was dried over magnesium sulfate. The dried ether solution was filtered to remove the drying agent and anhydrous HCl was bubbled in until precipitation of the hydrochloride of N'-methyl-2,6-dichlorophenylhydrazine was complete. The product was recrystallized from ethanol, yielding 30.5g. (67%) of N'-methyl-2,6-dichlorophenylhydrazine hydrochloride, m. p. 181-182°. Calculated for $C_7H_9N_2Cl_3$; C, 36.95%; H, 3.99%; N, 12.31%; Cl, 46.75%. Found: C, 36.84%; H, 3.89%; N, 12.36%; Cl, 46.61%. The infrared spectrum of the N'-methyl-2,6-dichlorophenylhydrazine hydrocholoride showed the following peaks: 3220(-NH), a broad peak centered at about 2930($-CH_3$), 2690 cm^{-1} ($-NH_2^{\oplus}$) (117), and a peak at 1560 cm-1 (aromatic C=C) (see Figure 8). The n.m.r. spectrum in D_2O showed peaks at 7.0τ($N-CH_3$), 5.3 τ(DOH), and an AB_2 pattern at 2.3 to 2.9 τ (see Figure 9).

6. 4-Chloro-3-nitrophenlhydrazine (118)

a. 4-Chloro-3-nitroaniline (132)

The hydrogen sulfate of p-chloroaniline was prepared by dissolving 51.2g. (0.40 mole) of p-chloroaniline in 400 ml. of concentrated sulfuric acid. The resulting solution of the sulfate was colled to -30° in a dry ice-acetone bath and 80 ml.

of concentrated nitric acid was added dropwise at such a rate that the temperature remained betwwen -20° and -30°. Upon completion of the addition of the nitric acid, the cooling bath was removed and the temperature was allowed to rise to -10°. The reaction mixture was poured into approximately an equal volume of ice, precipitating the sulfate of 4-chloro-3-nitroaniline. The sulfate was filtered and treated with sufficient sodium hydroxide to liberate the 4-chloro-3-nitroaniline. The product was recrystallized from hot water, yielding 47.6g. (65%) of 4-chloro-3-nitroaniline, m . p. 102 - 103°.

b. 4-Chloro-3-nitrophenylhydrazine (118)

A mixture of 12.5g. (0.073 mole) of 4-chloro-3-nitroaniline, 40 ml. of concentrated hydrochloric acid, and 40 ml. of water was warmed until the 4-chloro-3-nitroaniline dissolved. The mixture was then cooled to 0° and diazotized by adding a solution of 6g. (0.087 mole) of sodium nitrite in 15 ml. of water. The solution of the diazonium salt was filtered and added dropwise to a solution of 40 ml. of saturated ammonium sulfite and 12 ml. of concentrated ammonium hydroxide. After the solution was stirred for an half an hour, 70 ml. of concentrated hydrochloric acid was added and the resulting mixture stirred for an additional 8 hours. The hydrazine hydrochloride which had precipitated was separated by filtration, and then dissolved in 200 ml. of boiling water. The resulting solution was then filtered to remove small amounts of insoluble material and the filtrate was treated with a saturated solution

of sodium acetate to precipitate the hydrazine. The hydrazine was collected by filtration and immediately recrystallized from Skellysolve B. If the hydrazine was not recrystallized at once, decomposition resulted. Recrystallization yielded 6.2g. (45.3%) of 4-chloro-3-nitrophenylhydrazine, m. p. 108 - 109°. Reported m. p., 109°.

B. Preparation of Phenylhydrazones

1. Methyl Ethyl Ketone Phenylhydrazone (110)

A mixture of 14g. (0.2 mole) of methyl ethyl ketone and 21.6g. (0.2 mole) of phenylhydrazine in 50 ml. of ethanol was refluxed for one-half hour. The ethanol was removed by means of an aspirator and the residue was distilled under vacuum. The yield of methyl ethyl ketone phenylhydrazone was 24.6g. (76%), b. p. 160 - 163°/40 mm. Reported b. p., 190°/100 mm. (110).

2. Methyl Ethyl Ketone α-Methylphenylhydrazone

A mixture of 24.4g. (0.2 mole) of α-methyl-α-phenylhydrazine, 14g. (0.2 mole) of methyl ethyl ketone and 50 ml. of ethanol was heated under reflux for 1 hour. The ethanol was removed by means of an aspirator and the residue was distilled under reduced pressure. The yield of hydrazone boiling at 91 - 94°/12mm. was 13.0g. (40%). Reported b. p., 176 - 177°/135 mm. (110).

3. Cyclohexanone Phenylhydrazone

A mixture of 10.8 g. (0.1 mole) of phenylhydrazine, 9.81g. (0.1 mole) cyclohexanone and 50 ml. of

ethanol was refluxed for 1 hour. Upon evaporation of about half of the ethanol, 15.0g. (80%) of cyclohexanone phenylhydrazone crystallized, m. p. 75 - 77°. Reported m. p. 77° (133).

4. Methyl Ethyl Ketone 2,6-Dimethylphenylhydrazone

A solution of 3.4g. (0.02 mole) of 2,6-dimethylphenylhydrazine hydrochloride in 20 ml. of water was made basic with dilute sodium hydroxide and extracted with two 25 ml. portions of ether. The ether solution was dried over magnesium sulfate and the ether was evaporated on a rotary evaporator. To the residual oil was added a solution of 1.8g. (0.025 mole) of methyl ethyl ketone in 50 ml. of ethanol and the resulting mixture was refluxed for 1 hour. The ethanol was removed on a rotary evaporator. The viscous oil remaining after evaporation of the ethanol could not be induced to crystallize and darkened rapidly in air. Therefore, it was always used immediately without further purification. The yield of crude methyl ethyl ketone 2,6-dimethylphenylhydrazone was 3.2g. (84%).

5. Cyclohyexanone 2,6-Dimethylphenylhydrazone

A solution of 3.4g. (0.02 mole) of 2,6-dimethylphenylhydrazine hydrochloride in 20 ml. of water was made basic with dilute sodium hydroxide and extracted with two 25 ml. portions of ether. The ether extract was dried over magnesium sulfate and the ether was evaporated on a rotary evaporator. To the residual oil was added a solution of 1.96g. (0.02 mole) of cyclohexanone in 50 ml. of ethanol and the resulting mixture was refluxed for 1 hour. The solution was evaporated to about

half its volume and upon cooling, a pale yellow solid crystallized. The yield of cyclohexanone 2,6-dimethylphenylhydrazone was 3.7g. (86%), m. p. 38 - 40°. The compound darkened in air and was therefore always used immediately.

6. Cyclohexanone o-Chlorophenylhydrazone (79)

A solution of 2.85g. (0.02 mole) of o-chlorophenylhydrazine and 1.96g. (0.02 mole) of cyclohexanone in 50 ml. of ethanol was refluxed for 1 hour. The solution was reduced to about half its volume and upon cooling, cyclohexanone-o-chlorophenylhydrazone crystallized. The yield of product was 4.05g. (91%). The product melted at 49 - 50°. Reported m. p., 50.5°. The product decomposed if not used immediately.

7. Cylcohexanone 4-chloro-3-nitrophenylhydrazone (118)

A solution of 7.64g. (0.04 mole) of 4-chloro-3-nitrophenylhydrazine and 3.92g. (0.04 mole) of cyclohexanone in 50 ml. of ethanol was refluxed for 1 hour. Evaporation of the solution to about half its volume and subsequent cooling caused the product to crystallize. The crude product melted at 103 - 106°. Recrystallization from ethanol yielded 9.0g. (84%) of cyclohexanone 4-chloro-3-nitrophenylhydrazone, m. p. 106 - 107°. Reported m. p. 106 - 107°.

C. Cyclization of Phenylhydrazones

1. Cyclizations in the Presence of Dienophiles

a. Cyclization of Methyl Ethyl Ketone Phenylhydrazone

i. In Tetralin with Maleic Anhydride

A mixture of 16.2g. (0.1 mole) of methyl ethyl ketone phenylhydrazone, 49g. (0.5 mole) of maleic anhydride

and 100 ml. of tetralin was heated. When the temperature of the reaction mixture reached 120°, there was a sharp rise in temperature to 180°. Heating was discontinued and the mixture was allowed to cool to room temperature. A brown gummy solid separated. The tetralin was decanted and the gummy solid was dissolved in hot ethanol and treated with Norit. The Norit was removed by filtration and upon cooling, a pale yellow-solid crystallized; m. p. 253-258°. Three recrystallizations from ethanol raised the melting point to 261 - 262°. This compound proved to be maleinyl phenylhydrazide by a mixture m. p. determination with an authentic sample (94). Calculated for $C_{10}H_8N_2O_2$: C, 63.82%; H, 4.28%; N, 14.88%. Found: C, 63.63%; H, 4.36%; N, 14.82%. The yield of pure product was 8.1g. (43%). Extraction of the tetralin solution with sodium hydroxide and acidification of the basic extract failed to precipitate any other product.

ii. In Tetralin with Tetracyanoethylene

A mixture of 4.05g. (0.025 mole) and 3.2g. of tetracyanoethylene (0.025 mole) in 50 ml. of tetralin was refluxed for 1 hour. The tetralin was distilled under reduced pressure until the solution was about one-third its original volume. Upon cooling, a black solid precipitated, m. p. > 300°. Attempts to recrystallize and decolorize this material failed. No further attempt at characterization was made.

b. Cyclization of Methyl Ethyl Ketone α-Methylphenylhydrazone

A mixture of 8.2g. (0.05 mole) of methyl

ethyl ketone α-methylphenylhydrazone, 19.6g. (0.2 mole) of maleic anhydride, and 50 ml. of tetralin was heated under reflux for 6 hours. Upon cooling, a solid precipitated and proved to be unreacted maleic anhydride. Reduced pressure distillation of the filtered tetralin solution yielded 5.3g. (66%) of 1,2,3,-trimethylindole, b. p. 151 - 153°/10 mm. Reported b. p., 283-284°/750 mm. (110). Treatment of the residue from the distillation with dilute sodium hydroxide and acidification of the basic extract failed to produce a precipitate. When the volume of this aqueous solution was reduced nearly to dryness, more unreacted maleic anhydride precipitated.

c. Cyclization of the Diacetyl Derivative of Methyl Ethyl Ketone Phenylhydrazone

i. In Benzene with Maleic Anhydride

A mixture of 1.23g. (0.005 mole) of the diacetyl derivative of methyl ethyl ketone phenylhydrazone, 0.40g. of p-toluenesulfonic acid, 1.96g. (0.02 mole) of maleic anhydride, and 50 ml. of benzene was refluxed for 5 hours. The solution was allowed to cool to room temperature and was washed with dilute sodium hydroxide to remove the p-toluenesulfonic acid, any unreacted maleic anhydride, and any adduct which might have been formed. Acidification of the basic washings failed to produce a precipitate and extraction of this aqueous solution with ether and evaporation of the ether extracts, after drying, failed to produce any product. Evaporation of the benzene solution yielded a tan, foul-smelling solid, m. p. 101 - 104°. Recrystallization from ethanol yielded 0.27g.

(38%) of 2,3-dimethylindole, m. p. 103 - 105°. Reported m. p. 106° (102). A mixture m. p. determination with an authentic sample showed no depression.

ii. In Molten Maleic Anhydride

An intimate mixture of 12.3g. (0.05 mole) of the diacetyl derivative of methyl ethyl ketone phenylhydrazone and 19.6g. (0.2 mole) of maleic anhydride was placed in a sublimation apparatus and heated at 150° (bath temperature) for 1 hour, during which a large quantity of maleic anhydride sublimed onto the cold finger. The resulting mixture was allowed to cool and treated with a solution of 40% aqueous sodium hydroxide and the sodium hydroxide was decanted from the insoluble material remaining. The insoluble material was washed with water, dissolved in ethanol, treated with Norit, and cooled. A tan solid, m. p. 67 - 70°, was obtained. Three recrystallizations from ethanol yielded 3.63g. of 1-acetyl-2,3-dimethylindole, m. p. 70 - 72°. A mixture m. p. determination with an authentic sample showed no depression. Extraction of the sodium hydroxide solution with four 100 ml. portions of ether, evaporation of the dried ether extracts and recrystallization of the remaining material yielded 1.23g. of 1-acetyl-2,3-dimethylindole, m. p. 71 - 72°. The total yield of 1-acetyl-2,3-dimethyindole was 4.86g. (52%).

The aqueous sodium hydroxide solution was acidified with 6N hydrochloric acid and the pH was adjusted to 5.5 - 6.0 with aqueous sodium bicarbonate. The resulting solution was then extracted with ether in a continuous liquid-liquid extractor with 400 ml. of ether for 24 hours. Evaporation of

the dried ether extracts yielded ca. 30 mg. of a pale yellow solid, m. p. 98 - 100°. This product was soluble in dilute sodium hydroxide and could be reprecipitated with acid. Since the I. R. spectrum of this substance did not show any of the features expected of the dienone-imine maleic anhydride adduct, it was not characterized further.

2. Other Cyclizations

a. Cyclization of Methyl Ethyl Ketone Phenylhydrazone

A mixture of 16.2g. (0.1 mole) of methyl ethyl ketone phenylhydrazone and 100 ml. of tetralin was heated under reflux for 3 hours. The reaction mixture was allowed to cool and 30 - 60° petroleum ether was added in an attempt to precipitate the product. After the reaction mixture was kept in the refrigerator overnight, no product had precipitated. The solution was evaporated to ca. one-half its volume by reduced pressure distillation of the petroleum ether and tetralin. Again, petroleum ether was added and the mixture was allowed to cool overnight in the refrigerator. A brown solid precipitated. This solid was filtered, dissolved in a large volume of petroleum ether, decolorized with Norit and allowed to crystallize. A white, crystalline solid deposited which was found to be 2,3-dimethylindole. The yield of 2,3-dimethylindole was 6.1g. (42%), m. p. 104 - 105°. Reported m. p., 106° (102).

b. Cyclization of Methyl Ethyl Ketone-α-methylphenylhydrazone

A mixture of 8.2g. (0.05 mole) and 50 ml.

of tetralin was heated under reflux for 3 hours. The reaction mixture was then distilled under reduced pressure, yielding 4.93g. (63%) of 1,2,3-trimethylindole, b. p., 150 - 152°/10 mm. Reported b. p., 283 - 284°/750 mm. (110).

c. Cyclization of Cyclohexanone phenylhydrazone (113).

A solution of 9.40g. (0.05 mole) of cyclohexanone phenylhydrazone in 50 ml. of glacial acetic acid was boiled gently for 20 minutes. When the solution was allowed to cool to room temperature, white crystals separated. The solution was filtered and the crystals were washed on the funnel with several portions of water. The product was dried on the funnel under suction. The product melted at 117 - 119°. Recrystallization from aqueous ethanol yielded 7.4g. (86%) of 1,2,3,4-tetrahydrocarbazole, m. p. 118 - 119°. Reported m. p. 119°.

d. Cyclization of the Diacetyl Derivative of Methyl Ethyl Ketone Phenylhydrazone

A mixture of 1.23g. (0.005 mole) of the diacetyl derivative of methyl ethyl ketone phenylhydrazone, 0.40 g. of p-toluenesulfonic acid, and 50 ml. of benzene was refluxed for 3 hours. The benzene was removed on a rotary evaporator and the residue was washed with several portions of dilute sodium hydroxide. The residue was then recrystallized from ethanol, yielding 0.30g. (41%) of 2,3-dimethylindole, m. p. 103 - 105°. Reported m. p. 106° (102). A mixture m. p. determination with an authentic sample showed no depression.

When the above experiment was repeated, omitting the base wash of the residue, recrystallization from ethanol yielded a compound melting at 65 - 67°. Four recrystallizations from ethanol raised the m. p. to 71 - 72°. This compound proved to be 1-acetyl-2,3-dimethylindole. Reported m. p. 74° (102). Calculated for $C_{12}H_{13}NO$: C, 76.96%; H, 6.99%; N, 7.48%. Found: C, 76.77%; H, 6.90%; N, 7.43%. The infrared spectrum was identical to that of authentic 1-acetyl-2,3-dimethylindole (compare Figures 1 and 2) and a mixture m.p. determination with an authentic sample showed no depression.

e. Cyclization of Cyclohexanone o-Chlorophenylhydrazone (14)

To a solution of 11.1g. (0.05 mole) of o-chlorophenylhydrazone in 25 ml. of glacial acetic acid was added 7.1g. of boron fluoride-etherate in a dropwise fashion. The resulting mixture was refluxed gently for half an hour, during which ammonia-boron fluoride precipitated. The hot solution was filtered and the solid ammonia-boron fluoride was washed with two 5 ml. portions of hot acetic acid. The combined filtrate and washings were diluted with an equal volume of water and the product precipitated. The product was filtered and recrystallized from benzene-Skellysolve B, yielding 8.45g. (82%) of 8-chloro-1,2,3,4-tetrahydrocarbazole, m. p. 55 - 56°. Reported m. p., 56° (79). The product rapidly decomposed at room temperature if not kept in solution.

f. Cyclization Cyclohexanone-4-chloro-3-nitrophenylhydrazone (14).

The above procedures was repeated using 12.5g. (0.047 mole) of cyclohexanone-4-chloro-3-nitrophenyl-

hydrazone in 50 ml. of glacial acetic acid and 6.63g. (0.047 mole) of boron fluoride-etherate. After filtration of the ammonia-boron fluoride, the solid was washed with two 10 ml. portions of hot acetic acid. The combined filtrate and washings were diluted with an equal volume of water and a solid yellow mixture of 6-chloro-5-nitro-1,2,3,4-tetrahydrocarbazole and 6-chloro-7-nitro-1,2,3,4-tetrahydrocarbazole was obtained. This mixture was recrystallized repeatedly from ethanol until further recrystallization failed to raise the melting point. In this way, 5.21g. (44%) of 6-chloro-7-nitro-1,2,3,4-tetrahydrocarbazole was obtained, m. p. 186 - 187°. Reported m. p., 184° (118, 119). The filtrates from the methanol recrystallizations were combined and evaporated to dryness on a rotary evaporator. The yellow solid which remained was repeatedly recrystallized from benzene until further recrystallization failed to raise the melting point. The yield of 6-chloro-5-nitro-1,2,3,4-tetrahydrocarbazole was 1.32g. (11%), m. p. 162 - 163°. Reported m. p., 162° (118, 119).

D. Acetylation of Phenylhydrazones

1. Acetylation of Methyl Ethyl Ketone Phenylhydrazone (62)

A mixture of 25g. (0.154 mole) of methyl ethyl ketone phenylhydrazone, 159g. (1.54 mole) of acetic anhydride, and 0.64g. (0.004 mole) of p-toluenesulfonic acid monodyrate was refluxed for 1 hour. To the hot solution was added 0.30g. (0.004 mole) of anhydrous sodium acetate, the acetic anhydride was distilled off under reduced pressure and the residue was treated with 80 ml. of water. The resulting

mixture was extracted with four 100 ml. portions of ether, the combined ether extracts were dried over anhydrous magnesium sulfate, and the ether was evaporated on a rotary evaporator. The residue was distilled under reduced pressure, a fraction being collected at 167 - 169°/1.5 mm. The viscous, yellow distillate was dissolved in 15 ml. of absolute ether, 15 ml. of hexane was added and the product was allowed to crystallize in the freezing compartment of a refrigerator. The product melted at 53 - 56°. Recrystallization from absolute ether hexane yielded 21g. (55%) of the diacetyl derivative of methyl ethyl ketone phenylhydrazone, m. p., 57 - 58°. Reported m. p., 57 - 58°.

2. Acetylation of Methyl Ethyl Ketone 2,6-Dimethyl-phenylhydrazone

A mixture of 9.5g. (0.05 mole) of freshly prepared methyl ethyl ketone 2,6-dimethylphenylhydrazone, 51.0g. (0.5 mole) of acetic anhydride, and 0.19g. (0.001 mole) of p-toluenesulfonic acid monohydrate was refluxed for 1 hour. To the hot solution was added 0.08g. (0.001 mole) of anhydrous sodium acetate, the acetic anhydride was distilled off under reduced pressure and the residue was treated with 50 ml. of water. The resulting mixture was extracted with four 50 ml. portions of ether, the combined ether extracts were dried over anhydrous magnesium sulfate, and the ether was evaporated on a rotary evaporator. The residue was distilled under reduced pressure. The mixture darkened on heating, but a small quantity of material distilled at 172 - 174°/1mm. This colorless material crystallized in the receiver, m. p. 71 - 72°. Recrystallization

failed to raise this melting point. The product was shown to be N,N'-diacetyl-2,6-dimethylphenylhydrazine by Raney nickel-hydrazine reduction and identification of the resulting fragments (see Table I). Calculated for $C_{12}H_{16}N_2O_2$: C, 65.43%; H, 7.32%; N, 12.72%. Found C, 65.33%; H, 7.49%; N, 12.77%.

3. Acetylation of Cyclohexanone Phenylhydrazone

A mixture of 4.70g. (0.025 mole) of cyclohexanone phenylhydrazone, 25.5g. (0.25 mole) of acetic anhydride, and 4.76g. (0.025 mole) of p-toluenesulfonic acid monohydrate was stirred for 2 hours at room temperature. At the end of this period, 100 ml. of saturated aqueous sodium acetate was added and stirring was continued for another 2 hours. Then a solution of saturated aqueous sodium bicarbonate was added until the mixture was neutral. The mixture was then extracted with three 100 ml. portions of ether, the ether extracts were dried over anhydrous magnesium sulfate and the residue was chromatographed on neutral alumina. Elution with 1:1 hexane-benzene yielded 1.82g. of a crystalline compound, m. p. 75 - 77°. The compound was shown to be 9-acetyl-1,2,3,4-tetrahydrocarbazole by a mixed m. p. determination with an authentic sample. Calculated for $C_{14}H_{15}NO$: C, 78.84%; H, 7.09%; N, 6.57%. Found: C, 78.91%; H, 6.97%; N, 6.41%. The dark material remaining on the column could only be eluted with methanol and no pure substance could be isolated from these fractions.

4. Acetylation of Cyclohexanone 2,6-Dimethylphenylhydrazone

The preceding procedure was repeated using 5.65g. (0.025 mole) of freshly prepared cyclohexanone 2,6-dimethylphenylhydrazine, 25.5g. (0.25 mole) of acetic anhydride, and 4.76g. (0.025 mole) of p-toluenesulfonic acid monohydrate. At the end of the 2 hour stirring period, 100 ml. of saturated aqueous sodium acetate was added and stirring was continued for another 2 hours. Then a solution of saturated aqueous sodium bicarbonate was added until the mixture was neutral. The mixture was then extracted with three 100 ml. portions of ether, the ether extracts were dried over anhydrous magnesium sulfate and the residue was chromatographed on neutral alumina. Elution with benzene yielded 1.61g. of a crystalline compound, m. p. 90 - 92°. This compound was shown to be N'-acetyl-2,6-dimethylphenylhydrazine by Raney nickel-hydrazine and identification of the fragments (see Table I). Calculated for $C_{10}H_{14}N_2O$: C, 67.50%; H, 7.91%; N, 15.72%. Found: C, 67.51%; H, 7.95%; N, 15.20%.

E. Condensation of Cyclohexanone with N'-Methyl-2,6-dichlorophenylhydrazine

1. In Refluxing Benzene

A solution was prepared by dissolving 6.84g. (0.03 mole) of N'-methyl-2,6-dichlorophenylhydrazine hydrochloride in water. The resulting solution was made basic with dilute sodium hydroxide and the oil which separated was extracted with two 25 ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, the ether was evaporated

on a rotary evaporator, and the residue was dissolved in 50 ml. of benzene. To this benzene solution was added 2.94g. (0.03 mole) of cyclohexanone and the resulting mixture was refluxed, using a Dean-Stark trap to collect the water formed. When no more additonal water appeared in the trap (ca. 40 minutes), refluxing was discontinued. It was noticed that a precipitate had settled from the solution. The benzene solution was allowed to cool to room temperature and the precipitated solid was filtered. This white solid melted at 180 - 189°, was water soluble, and an aqueous solution of the material gave a precipitate with aqueous silver nitrate. When an aqueous solution of this material was made basic, a gas with an ammonia-like smell was evolved. Recrystallization from ethanol several times raised the melting point to 221 - 224°. This compound was shown to be methylamine hydrochloride by a mixed m. p. determination and comparison of the n. m. r. spectrum with that of authentic material. The yield of recrystallized material was 0.33g. Evaporation of the benzene from the filtrate gave a yellow oil which darkened in air. Attempts to crystallize this oil failed.

2. In Benzene at Room Temperature

A solution was prepared by dissolving 6.84g. (0.03 mole) of N'-methyl-2,6-dichlorophenylhydrazine hydrochloride in water. The resulting solution was made basic with dilute sodium hydroxide and the oil which separated was extracted with two 25 ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, the ether was evaporated

on a rotary evaporator, and the residue was dissolved in 50 ml. of benzene. To this benzene solution was added 2.94g. (0.03 mole) of cyclohexanone and the resulting mixture was slowly evaporated on a rotary evaporator (bath temperature, 20°) until approximately half of the benzene has evaporated. Methylamine hydrochloride precipitated, was filtered off, and recrystallized from ethanol. The yield of methylamine hydrochloride melting at 222 - 225° was 0.30g. (14.8%). The remainder of the benzene solution was evaporated and the yellow oil which remained was chromatographed on neutral alumina. Elution with Skellysolove B yielded a pale yellow solid, m. p. 55 - 56°. This compound was shown to be 8-chloro-1,2,3,4-tetrahydrocarbazole by a mixture m. p. determination with an euthentic sample and examination of the infrared and n. m. r. spectra. The infrared spectrum showed a bonded -NH band (3100 cm^{-1}) and the n. m. r. spectrum showed methylene peaks at 7.29 τ and 8.20 τ and an -NH peak at 1.38 τ. The sample was too unstable to be sent for analysis. The yield was 0.86g. (14.0%). Further elution with 1:1 Skellysolve B-benzene yielded a tan crystalline solid, m. p. 87 - 90°. Recrystallization from ethanol gave colorless crystals, m. p. 90 - 91°. This compound was shown to be 5-amino-6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole by mixture m. p. determination and comparison of the n. m. r. spectrum with that of an authentic sample. The n. m. r. spectrum showed an aromatic AB pattern at 3.0 - 3.8 τ, and $-NH_2$ peak at 5.9 τ, an N-methyl peak at 6.75 τ, and methylene peaks at 7.24, 7.58, and 8.30 τ (compare Figs. 10 & 11). The yield was 1.48g (21%). Calculated for

$C_{13}H_{15}N_2Cl$: C, 66.51%; H, 6.44%; N, 11.94%; Cl, 15.11%.
Found: C, 66.59% ; H, 6.49%; N, 11.75%; Cl, 15.37%.

Further elution of the chromatography column with benzene and benzene-ether mixtures failed to separate any material from the column. Elution with ether rapidly caused the dark material remaining on the column to come off and no further pure compounds could be obtained even when an attempt was made to chromatograph this material again.

F. Raney Nickel-Hydrazine Reductions

1. Preparation of W-2 Raney Nickel (124)

A solution of 38g. of sodium hydroxide in 150 ml. of distilled water was cooled to 10° and stirred while 30g. of nickel-aluminum alloy was added in small protions. The alloy was added at such a rate that the temperature did not rise above 25°. When all the alloy had been added, stirring was discontinued, the reaction mixture removed from the cooling bath and allowed to come to room temperature. After the evolution of hydrogen became slow, the reaction mixture was heated on a steam bath until the evolution of hydrogen again became slow. After heating, the nickel was allowed to settle and most of the liquid was decanted. Distilled water was added to bring the solution to its original volume, the nickel was suspended by stirring, allowed to settle and the water was again decanted. A solution of 5.0g. of sodium hydroxide in 50 ml. of distilled water was added, the resulting mixture was stirred, the nickel was allowed to settle, and the alkali was decanted. The nickel was washed by suspension in distilled water and decantation until the washings were neutral to litmus

and then 10 times more to remove the alkali completely. Washing was repeated with three 20 ml. portions of 95% ethanol, followed by washing with three 20 ml. portions of absolute methanol. The catalyst was then stored under absolute methanol until used.

2. Reduction Procedure (112)

The following general procedure was used for all reductions. A solution of 50 ml. of methanol, containing 1g. of the acylated phenylhydrazine and about 1g. of W-2 Raney nickel was stirred vigorously and gently refluxed for a period of 1 hour during which time an excess of hydrazine hydrate was added dropwise. At the end of the reaction time the catalyst was separated by filtration, and the solvent removed under reduced pressure. The product, crystallized from a suitable solvent, was identified by its melting point and mixed melting point with an authentic sample. With those compounds which yielded acetamide as one product, the residue obtained after removal of solvent was treated with 20 ml. of cold water to dissolve and thus remove the acetamide. The mixture was then filtered and the aqueous filtrate was evaporated to obtain the acetamide.

G. Other Preparations

1. Maleinylphenylhydrazide (94)

A mixture of 5g. (0.051 mole) of maleic anhydride and 5.5g. (0.051 mole) of phenylhydrazine was refluxed in 30 ml. of glacial acetic acid for 20 minutes. The reaction mixture was poured into water and crystallization of the

resulting precipitate from ethanol yielded 4.2g. (44%) of maleinylphenylhydrazide, m. p. 260 - 261°. Reported m. p. 260° (95).

2. 1-Acetyl-2,3-dimethylindole (102)

A solution of 25g. (0.17 mole) of 2,3-dimethylindole in 100 ml. of acetyl chloride was refluxed for 4 hours. The excess acetyl chloride was removed under reduced pressure and the residue distilled at 155°/1 mm. The distillate, which solidified on cooling, was recrystallized from ethanol to yield 23.3g. (73%) of 1-acetyl-2,3-dimethylindole, m. p. 71 - 72°. Reported m. p., 72°.

3. 9-Acetyl-1,2,3,4-tetrahydrocarbazole (113)

A solution of 8.5g. (0.05 mole) of tetrahydrocarbazole in 30 ml. of acetic anhydride was refluxed for 6 hours. The excess acetic anhydride was removed under reduced pressure and the residue distilled at 137°/1 mm. The distillate, which solidified on cooling, was recrystallized from aqueous ethanol to yield 7.5g. (71%) of 9-acetyl-1,2,3,4-tetrahydrocarbazole, m. p. 75 - 77°. Reported m. p. 77°.

4. Methylation of 6-Chloro-5-nitro-1,2,3,4-tetrahydrocarbazole (29)

A solution was prepared by dissolving 1.32g. (0.005 mole) of 6-chloro-5-nitro-1,2,3,4-tetrahydrocarbazole in 15 ml. of acetone. To this solution was added 1.5 g. of potassium hydroxide in a little water and 1.5 ml. of methyl sulfate and the resulting mixture was shaken mechanically for 4 hours. The mixture was then diluted with water, pre-

cipitating the product. Recrystallization from ethanol yielded 0.81g. (61%) of 6-chloro-5-nitro-9-methyl-1,2,3,4-tetrahydrocarbazole, m. p. 154 - 155°. That the nitrogen at the 9-positon had been methylated was shown by the disappearance of the -NH peak at 4.94 τ which was present in the n. m. r. spectrum of the starting material and the appearance of an $N-CH_3$ peak at 6.65 τ in the n. m. r. spectrum of the product. Calculated for $C_{13}H_{13}N_2O_2Cl$: C, 58.98%; H, 4.95% N, 10.59%; Cl, 13.40%. Found: C, 59.09%; H, 5.19%; N, 10.50%; Cl, 13.21%.

5. Reduction of 6-Chloro-5-nitro-9-methyl-1,2,3,4-tetrahydrocarbazole (111)

A solution of 0.75g. (0.003 mole) of 6-chloro-5-nitro-9-methyl-1,2,3,4-tetrahydrocarbazole in 15 ml. of methanol containing approximately 0.5g. of W-2 Raney nickel, was refluxed while 5 ml. of hydrazine hydrate was added dropwise. The addition of the hydrazine hydrate was discontinued when the yellow solution became colorless. The hot solution was filtered to remove the catalyst and the filtrate was evaporated, giving a colorless compound. Recrystallization from ethanol yielded 0.55g. (79%) of 5-amino-6-chloro-9-methyl 1,2,3,4,-tetrahydrocarbazole, m. p. 90 - 91°. The n. m. r. spectrum showed the following peaks: an aromatic AB pattern at 3.0 - 3.8 τ, an $-NH_2$ peak at 5.9 τ, an N-methyl peak at 6.75 τ, and methylene peaks at 7.24, 7.58 and 8.30 τ (see Figure 11). Calculated for $C_{13}H_{15}N_2Cl$: C, 66.51%; H, 6.44%; N, 11.94%; Cl, 15.11%. Found: C, 66.64%; H, 6.57%;

N, 12.18%; Cl, 14.98%. An acetyl derivative was prepared by dissolving 0.20 g. of the 5-amino-6-chloro-9-methyl-1,2,-3,4-tetrahydrocarbazole in the least possible amount of benzene, adding 10 drops of acetic anhydride, and warming the resulting mixture on the steam bath for 10 minutes. The colorless crystals which separated on cooling were filtered and recrystallized from ethanol. The acetyl derivative melted at 245°. Calculated for $C_{15}H_{17}N_2ClO$: C, 65.09%; H, 6.18%; N, 10.11%; Cl, 12.81%. Found: C, 65.24%; H, 5.96%; N, 10.29%; Cl, 13.09%.

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